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JUNE

ALFRESCO REPAST

We derive from both art and literature the impression that picnics were once marked by a formality and a decorum which they lack today. How gracefully those crinolines billow upon the greensward! How attentively the young gentleman in tight breeches proffers what is quite possibly a bowl of syllabub to the lady in mauve! With what zeal are those two footmen in the background unpacking yet another hamper of viands!

Things are much different when we have a picnic. The *venue* selected for the purpose appears idyllic. It is only after we have settled down that cows appear from nowhere to blow meditatively down the backs of our necks and we discover that the rug is spread over a densely populated colony of ants. The manners of our party lack that stylized courtliness which the artists were at pains to emphasize; we cannot, for instance, imagine the lady in mauve saying "Chuck us a scone" or "After you with the teaspoon".

There is, however, no future in regretting the past, and still less, as far as picnics are concerned, in trying to ape it. Even if we had those two footmen, there would be no room for them in the car. We know that we must cut our coat according to our cloth; and the same sort of thing applies to sandwiches.

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 5 1954

THE DYNAMICS OF HAEMOPOIESIS*

BY

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Even the most casual survey of the activities of the haemopoietic system, which has to maintain a constant population of erythrocytes, leucocytes, platelets, and other factors in the face of losses caused by daily wear and tear, can leave no doubt that the system is highly dynamic. It is perhaps not inappropriate that I should have chosen this title for the Thomas Huxley Lecture, since Huxley himself, who qualified from this great school in 1845, was a most dynamic personality. I propose to present, in a necessarily most limited survey, a few of the active features of the haemopoietic system in the light of my experiences and work, as well as my considered opinion of the work of others; and I shall try to make some estimate of the nature and magnitude of the task of providing and renewing a normal population of blood cells. This will necessarily call for some survey of the physiological processes of blood formation.

It is fortunate, perhaps, so far as dynamic studies are concerned, that the many mobile cells of the haemopoietic system have an unmistakable appearance or a unique composition which enables something of their life histories to be accurately followed by cytochemical, serological, and radioactive techniques, and by these means some estimate has been made of what is required in everyday life, as well as in times of stress.

The active bone marrow in the average adult is estimated to weigh some 3,000 g. (3.5–6% of body weight, or 1,500–3,500 g.); it roughly equals the weight of the liver; its volume is large, being some 70 ml. at birth and about 4,000 ml. when the subject is full-grown. In the adult, however, only about half the marrow is in an active state, but it has an enormous reserve of functional capacity, as well as considerable room for expansion. The parent cells of the marrow can produce many times their own volume of mature cells in a relatively short time.

The Erythron

So far as the erythron (Fig. 1) is concerned the 3,000 g. of bone marrow makes use of the amino-acids derived from the protein pool and of iron derived from the catabolism of effete red cells, as well as some of that which is absorbed from the intestine, and a little of that which is contained in the iron stores, in order to maintain a circulating erythrocyte population of some 25 million millions (25×10^{12}).

There is good evidence that in a normal person the life-span of the red corpuscle is some 120 days.

The task of maintaining the erythrocyte population, the replacement of 1/120 each day, amounts, therefore, to approximately 2.1×10^{11} corpuscles a day, or about 9,000 millions in an hour. This involves the incorporation of 6.5 g. of haemoglobin (each gramme containing 3.34 mg. of iron) a day on the production side, whilst the daily destruction of cells leads to the liberation of about 20–26 mg. of iron, together with porphyrin and globin.

The process of red-cell destruction is carried out by the reticulo-endothelial system, itself being about half the weight of the marrow, from whence the iron and globin are used again, whereas the porphyrin pigments, appearing in the bile, are excreted mainly in the faeces as some 250 mg. of faecal urobilinogen a day. Excretion, however, is very variable, and it is difficult to obtain correlation between corpuscular destruction and pigment excretion.

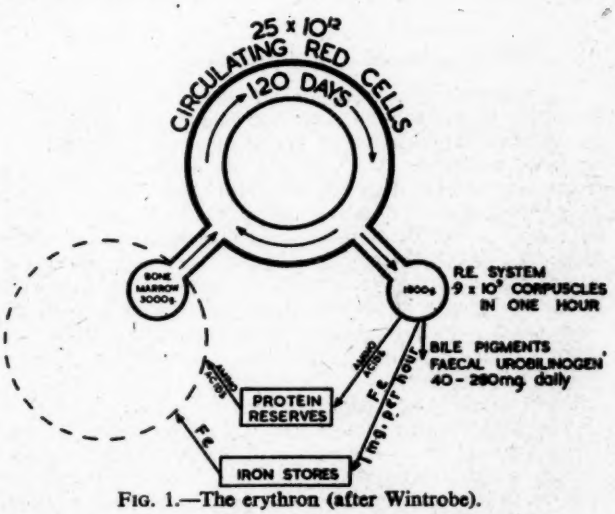


FIG. 1.—The erythron (after Wintrobe).

On the other hand, the amount of iron which is excreted is minimal, and is fairly precisely known, being a daily amount of from 0.6–0.8 mg. in the bile (Hawkins and Hahn, 1944) and 0.4–0.6 mg. in the urine (Barer and Fowler, 1937) according to sex. In all estimations, however, the fact that women suffer an iron loss of 10–40 mg. at each menstrual period, or about 1 mg. a day over the whole menstrual cycle, has to be borne in mind, since it means that women lose about twice as much iron as men.

Pregnancy, a physiological process, almost doubles the figure, but lactation adds no more than 1.5 mg. to the normal daily loss, unless menstruation becomes re-established, whereupon the total iron loss becomes almost as great as in pregnancy.

In effect, some nine-tenths of the dry weight of the red cell consists of haemoglobin, and this is contained in a complex stroma, itself a unique combination of

*Thomas Huxley Lecture delivered at Charing Cross Hospital Medical School on March 18.

protein and lipids together with such specific factors as blood-group substance as well as enzymes, minerals, and other substances. The whole comprises a cell which is one of the most specialized structures in the mammalian organism, a cell whose functional activity is carried on for months after its nucleus has been lost, and with such efficiency that it consumes practically none of the oxygen which it transports.

This simplified and elementary summary of the everyday dynamics of erythropoiesis underlies the basic pathology of all anaemias, for when the pace is not maintained then anaemia occurs—that is, when blood loss or blood destruction outstrips the daily production (Whitby, 1937). And the principle is the same whether the blood loss is obviously direct, as with haemorrhage or a violent haemolytic process, or whether it is no more than the physiological hourly blood loss of some 9,000 million cells, to which I have already referred.

Failure to keep pace with the physiological blood loss may be due to very many causes. Some of these are trivial, some are serious, some curable, others incurable, and they may operate with different intensities, and singly or in combination, to reduce the efficiency of the process of blood formation to various degrees; these causes include everything in the vast field of what used to be called secondary anaemias. A proper understanding of these different stresses demands some knowledge of the processes involved in haemoglobin synthesis, iron balance and metabolism, red-cell production, and red-cell maturation.

Haemoglobin Synthesis

The synthesis of haemoglobin requires supplies for the formation of the sub-units and the building up from these of the main components of haemoglobin; in this process enzymes, hormones, vitamins, and other substances play a large part. Globin is synthesized from natural amino-acids; its availability is not usually impaired except by gross dietary deficiency of one or more of the ten essential amino-acids. Moreover, the deficiency has to be sustained and severe before globin formation is reduced, because the body preferentially breaks down even its own proteins to provide amino-acids for haemoglobin formation, rather than that there should be a globin deficiency. Tissue respiration is indeed a primary vital function.

The synthesis of haem requires adequate supplies of porphyrin precursors and of iron. Two porphyrins (I and III) are found in nature and in the animal body. In the human subject these porphyrins are synthesized and are not, as in some animals, derived from preformed pyrroles such as chlorophyll.

When haemoglobin is catabolized the porphyrins are not used again as such, but the iron which they contain is mainly conserved and, indeed, forms the major part of the iron used for the daily requirements of haemoglobin, since it appears to be preferentially used before either the iron which is absorbed from the intestine or that which is contained within the body stores. Nevertheless, as a protection against stress, the iron reserves of the body are very considerable, a fact which becomes obvious when one realizes the speed with which a patient who has suffered a moderate haemorrhage can regenerate his blood without supplementary iron treatment.

Iron Stores

Hynes (1949) found that the iron stores in a normal man probably amounted to some 600 mg., which is sufficient to replace about one-quarter of the circulating haemoglobin in times of need. This estimate agrees with the clinical observation that a haemorrhage of roughly this order is the largest amount from which recovery is readily possible without supplementary iron treatment.

We have made a fairly close study of children in my department in order to arrive at some estimate of the amount of iron required by growing children to furnish an adequate tissue store. Because the blood volume increases with growth and because the tissue stores likewise enlarge, the growing child requires considerably more iron than the adult. We have estimated that infants, during the first year of life, need to lay down an additional store of some 200 mg. of iron, the amount falling to 100 mg. annually in the third year, and remaining at this figure until about the ninth year, when growth begins to increase rapidly. The amount of iron then laid down rises to about 350 mg. at the age of 17, and thereafter declines to zero at 21, when growth ceases.

The building up of iron stores is, however, by no means a straightforward process, since the manner in which iron is absorbed from the intestine and the form in which that which is derived from the catabolism of red cells or from intestinal absorption is transported to the various stores within the body, or, from the stores, to be incorporated in the haem molecule, is one of the processes in iron metabolism which are by no means simple.

Transport of Iron

At any one time the total serum iron of a normal man is about 4 mg., whilst every day some 20–26 mg. of iron leaves the blood stream, and of this about four-fifths is taken up by the marrow. This is used for the immediate daily requirement in haemoglobin synthesis, whilst the excess is stored primarily and mainly in the liver. In order to transport the amount of iron required for normal daily haemoglobin synthesis the iron in the plasma must therefore be turned over some five times a day.

The marrow is very active in removing serum iron from the blood. Theoretical calculations suggest that during increased haemopoietic activity more than 10% of the plasma iron passing through the bone marrow may be retained (Laurell, 1952), and since this iron in process of transport—so-called Fe-transferrin, a plasma-globulin—is mainly derived from the catabolism of red cells, and is rapidly used again, it follows that the iron stores of the body are turned over relatively slowly. The main cycle of iron turnover is from the plasma to the newly formed cells and from the old catabolized cells back to the plasma.

Thus the level of plasma iron in the blood represents an equilibrium among a number of dynamic processes which include the rate of haemoglobin breakdown and the release of iron therefrom, the rate of uptake of iron by the marrow for the synthesis of haemoglobin, the rate of removal of iron from the blood stream for storage in the tissues, the rate of formation and decomposition of transferrin itself, as well as the degree to which it is saturated with iron. This last point enters into the field of practical clinical medicine, since the level of plasma iron and the degree of iron saturation are considered to be sensitive and reliable indices of iron deficiency or iron excess.

For example, it is generally found that transferrin is saturated with iron in diseases, such as haemochromatosis, in which iron is in excess; or when haemoglobin catabolism is active, as with the haemolytic anaemias; or when the marrow needs iron but cannot use it properly, as with pernicious anaemia.

On the other hand, transferrin remains very unsaturated with iron when the bone marrow is highly active in a physiological manner, as with acute haemorrhage and iron-deficiency anaemia.

Absorption of Iron

From the aspect of physiology, as well as practical therapeutics, the control of iron absorption represents one of the key points in iron balance and iron metabolism. This likewise is not simple. A single guiding principle determines

the maintenance of iron balance—namely, that to the human body iron is a precious metal which is carefully conserved. Excretion is minimal.

Iron balance is maintained by a regulation of absorption according to the needs of the body, rather than by the excretion of unwanted excess. If this were not so, then every aged person would suffer from haemochromatosis. Sufficient iron to balance the small daily excretion is ordinarily derived from everyday foodstuffs, some of which contain reasonable quantities of the metal and others a negligible amount, and there is abundant evidence (Moore *et al.*, 1944) that ferrous iron is absorbed twice as effectively as ferric.

Without entering into detail, one may say that in certain foods iron is more available than in others, that valency and reaction, such as the difference between achlorhydria and normochlorhydria, affect absorption, and that an iron-free protein in the intestinal mucosa—apoferritin—can become appropriately and variously saturated with iron to form ferritin, according to body needs, until no more can be absorbed. This enters the plasma to contribute to the transferrin therein, and to be deposited therefrom in the tissue depots as ferritin once again.

It is instructive to note that, in experimental iron-deficiency anaemias, neither ferritin nor apoferritin can be detected in the cells of the intestinal mucosa, but that both quickly appear when iron feeding is instituted. This leads to the attractive theory that apoferritin is specifically formed in response to the stimulus supplied by the presence of ionized iron in the gut.

It would seem that ionic iron in the mucosal cell is in equilibrium with the plasma iron and this, in turn, with the iron in ferritin in the store depots. Thus, when the ionic iron in the mucosa attains a certain level, a state of mucosal block occurs and continues until the level of ionic iron in the cells falls low enough to allow more iron to be absorbed.

Utilization of Iron

Because of all the factors which govern the movement and utilization of iron, it is not easy to translate practical therapeutic principles into simple mathematical expressions, since the theoretical requirements are greatly influenced by such matters as absorption, route of administration, the nature of the preparation, and the extent to which its iron content is utilized.

An adult with 100% of haemoglobin has from 750–900 g. of circulating haemoglobin containing from 2.5–3 g. of iron. In order to replenish each 1% of haemoglobin deficiency, the body must absorb and utilize some 25 mg. of iron. Ferrous salts, the best preparations, are used only to the extent of about 15%. One gramme of anhydrous ferrous sulphate contains 360 mg. of iron, and if 10% of this is utilized the administration should cause a rise of about 2% in the circulating haemoglobin.

Practical experience has shown that there is no advantage in giving more than 2 g. of ferrous sulphate a day, which ought to ensure a rise of 4%. It is not justifiable, however, to assume that iron given to anaemic patients in optimal doses will be absorbed in accordance with the theoretically expected utilization; in that, with iron deficiency, it is often absorption which is at fault.

Many patients also do not respond to ingested iron, and it is quite useless to increase the dose beyond the optimum. On the other hand, with intravenous iron, the whole is absorbed and is rapidly available for utilization provided the pathological process is not such as to inhibit it.

In some circumstances the utilization may amount to as much as 80% (Whitby, 1949), causing an apparent increase in haemoglobin of threefold or more. I have deliberately said "apparent," since every now and again we become aware of the fact that figures obtained from samples of the peripheral blood are relative rather than absolute, and that they may be fallacious unless they are converted into total figures by means of a blood-volume determination.

Table I (a case of gross iron deficiency) is a simple illustration of this point, since it reveals the fallacy of estimating iron utilization by the peripheral blood figure alone without reference to the total haemoglobin as determined by the blood volume. Whereas the former shows an increase of the order of 100% (from 6.7 to 13.3 g. per 100 ml.), the latter shows the true increase to be 160% (from 190 g. to 490 g.).

TABLE I.—*Absorption and Utilization of Iron in Patient Weighing 50 kg. (Ferrous Sulphate=600 mg. Iron Daily)*

Day of Treatment:	0	9	23	49
Hb (g. per 100 ml.) ..	6·7	8·3	10·5	13·3
Increase Hb	—	24%	57%	100%
Plasma vol. (ml.) ..	2,120	2,250	2,410	2,100
Corpuscular vol. (ml.)	710	1,060	1,290	1,590
Total blood vol. (ml.) ..	2,830	3,310	3,700	3,690
Total Hb (g.)	190	280	390	490
Increase in total Hb ..	—	47%	105%	160%

In theory, a patient with pernicious anaemia should have no need for iron, in that the haemoglobin was once normal and almost all the iron derived from the cells during the course of destruction is retained in the body. But we (Whitby and Britton, 1953) have found that some 40% of patients with pernicious anaemia require iron as judged by the mean corpuscular haemoglobin concentration, and, so far as women are concerned, a great number are iron-deficient before they contract pernicious anaemia.

Table II shows the very large amount of iron that is utilized during the cure of pernicious anaemia, as well as the adjustments in corpuscular and plasma volumes which occur at the same time; the patient, a small woman of some 45 kg., used as much as 1.34 g. of iron with a four-fold increase in total haemoglobin, and at the same time an initial high plasma volume became readjusted to a lower figure coinciding with an increase in corpuscular volume, though the total blood volume remained virtually the same.

TABLE II.—*Iron Requirements in Pernicious Anaemia. Female Weighing 45 kg.*

Day of Treatment:	0	50
Haemoglobin (g. per 100 ml.) ..	3·9	14·0
Plasma vol. (ml.)	3,070	2,300
Corpuscular vol. (ml.)	400	1,500
Total blood vol. (ml.)	3,470	3,800
Total haemoglobin (g.)	130	530
Total iron (mg.)	434	1,770

It is unfortunate that there is no simple method, indeed no method entirely free from fallacies and objections, for the determination of blood volume, since an accurate appreciation of the movements and alterations in cells and plasma would be of great value in clinical medicine.

Erythropoiesis under Stress

The examples which I have given illustrate some of the features associated with the utilization of iron, but they also serve to show that even under apparently straightforward conditions the mathematics of iron balance may be complex.

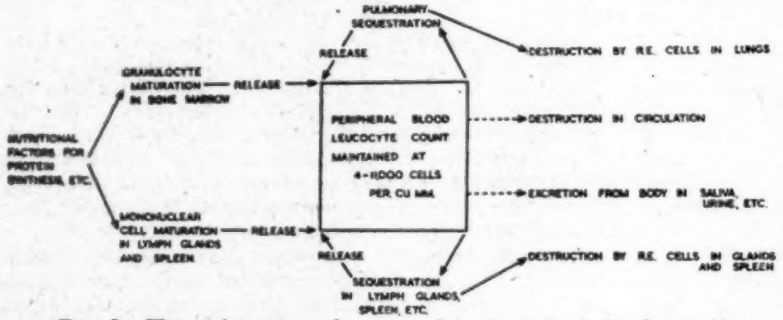
Numerous factors may indeed intrude to upset a simple calculation, and even though as a basic principle it can be accepted that many anaemias are due to the fact that production fails to keep pace with the physiological but negative side of the iron-balance equation, it is axiomatic that a gross negative imbalance could not endure for long, otherwise the subject would soon have no red cells at all. This can be well illustrated by the dynamic activity that lies behind the clinical syndrome of haemolytic anaemia.

If the volume of the circulating cells is to remain constant, then production and destruction must be equal, even though the organism may need to adapt itself to a diminished population or to a population of cells ill-equipped to perform their proper function, assuming that both such

populations are composed of cells having a normal survival time.

When the negative side is rapidly increased, as with blood loss or violent haemolysis, balance can be maintained only by compensatory hypertrophy. When, therefore, as is usual in many of the haemolytic anaemias, the average red cell survives for a significantly, sometimes very considerably, less time than the normal average of 120 days, the degree of compensatory hypertrophy needs to be great, and may, indeed, be more than the latent reactive powers of the marrow can accomplish.

Crosby (1954) has given some instructive figures illustrating this point. Thus the function of the red marrow is to maintain a constant level of circulating red cells, and for this purpose, to quote Crosby, "Ten red cells that survive twelve days are equivalent to one red cell that survives 120 days, so that, to maintain a normal level with short-lived twelve-day erythrocytes the marrow would have to produce each day ten times the normal number."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RELEASE
RELEASE
DESTRUCTION BY R.E. CELLS IN GLANDS AND SPLEEN
SEQUESTRATION IN LYMPH GLANDS, SPLEEN, ETC.

FIG. 2.—The maintenance of a normal level of circulating leucocytes.

In certain circumstances, both factors—red-cell survival and marrow function—may contribute to the production and maintenance of a severely anaemic state—namely, cells which have a short survival time, which are destroyed by random selection rather than by virtue of age, and a marrow which is incapable of an adequate response.

Another example is pernicious anaemia, when the life-span of the red cells is about 30 days (about one-quarter of the normal period), and it is perhaps difficult to appreciate that even though the bone marrow utilizes as much as 17 g. of haemoglobin a day, or two and a half times normal, the hypertrophy is insufficient to maintain the red-cell count at a normal level.

In congenital haemolytic icterus the utilization of haemoglobin by the hyperplastic marrow is even greater. This is because the spherocytes have the short survival time of some 12 days only, and because at times of an aregenerative (sometimes called aplastic) crisis the marrow cannot keep pace with the demands. The degree of anaemia may then rapidly become severe.

The Leucon

Leucopoiesis is also highly dynamic. The number of leucocytes needed to replace daily losses and maintain the circulating cells within the normal range has been studied frequently and by many methods, but the estimates made of the normal life-span of the different leucocytes vary widely. Studies in parabiotic rats (van Dyke and Huff, 1951) gave times as short as 23 minutes for the average neutrophil and 170 minutes for a lymphocyte. White (1954), however, estimated the intravascular life-span of transfused neutrophil leucocytes, tagged with mepacrine, to be from 30 to 90 minutes.

At the other end of the scale, when using radioactive phosphorus, the average survival time of the neutrophil polymorphonuclear in a normal subject was estimated (Kline and Cliffton, 1952) to be thirteen days. Many other intermediate values have been obtained by different methods, and it is not possible in the present stage of knowledge to make more than a rough estimate of daily leucocyte loss. The lowest figure must be of the order of 1,000 million leucocytes, and the highest may be as much as a million million. But as an approximate compromise, if it be accepted that the life of the neutrophil polymorphonuclear does not exceed five days, it is necessary for the marrow to replace at least some 5,000 million neutrophils each day, and if lymphocytes have a life-span of less than one day then the daily replacement figure needs to be some 3,000 millions.

With leucocytosis and leukaemia, in which the circulating leucocytes are greatly increased in number, the task of production is probably more exacting, though there is some evidence (Kline and Cliffton, 1952; White, 1954) that the life-span of leukaemic leucocytes is several times that of the normal cell.

Leucocytic production, whether physiological or pathological, demands the synthesis and new formation of the basic fundamental substances comprising the cell. Cytochemical studies have shown that multiplication is associated with an intensive production of protein within the cells.

Granular leucocytes also contain considerable amounts of phospholipids and glycogen, as well as numerous enzymes, including trypsin, lipase, amylase, catalase, alkaline phosphatase, esterase, and oxidase.

Some of the factors concerned with and the processes involved in maintaining a normal leucocyte count are shown in Fig. 2. In general, there is a balance between production by the marrow and reticulo-endothelial system; sequestration in the lungs, lymph nodes, and spleen; and destruction in these same sites as well as in the circulation itself.

Nutritional Factors in Leucopoiesis

Nutritional deficiencies of various kinds have been found to cause defective formation of leucocytes under experimental conditions.

Several investigators (Daft, 1947; Guggenheim and Buechler, 1949) found that a protein-free diet would produce severe leucopenia in experimental animals which could be corrected with a diet containing optimum amounts of protein or amino-acids. The effectiveness of different proteins for regenerating leucocytes under such experimental conditions appears to bear some relation to efficiency in growth promotion, suggesting that the same amino-acids are necessary for growth as for leucopoiesis. Deficiencies of tryptophan (Cartwright *et al.*, 1945), pantothenic acid (Ashburn *et al.*, 1947), and riboflavine (Endicott *et al.*, 1947) will cause leucopenia which can be corrected with folic acid. Presumably the leucopenia of pernicious anaemia is due to a nutritional deficiency, since it responds to treatment of the disease with folic acid, citrovorum factor, or vitamin B_{12}.

Control of Leucopoiesis

The mechanism for the physiological control of leucopoiesis is unknown. Nervous and hormonal factors have been surmised, but there is little experimental or clinical evidence in support of such views. Corticotrophin and adrenal corticoids appear to influence the peripheral leucocytes in some way, but Rosenthal *et al.* (1951) found no alteration in bone-marrow cellularity or differential cytology as the result of treating human subjects with these steroids. Nevertheless, both corticotrophin and cortisone sometimes have a stimulating action on the marrow in cases of agranulocytosis.

The question of the existence of a splenic hormone is of interest, but the available evidence, such as the large leucocytosis which immediately follows splenectomy, suggests that any splenic controlling effect is on release of cells into the circulation rather than directly upon production and maturation.

For the past fifteen years Menkin (1940, 1949) has consistently studied certain substances present in inflammatory exudates, which affect not only the maturation of leucocytes but also their release into the circulation. These leucocytosis-producing and leucopenia-producing agents have, in Menkin's hands, caused hyperplasia and hypoplasia of myeloid marrow elements when injected into experimental animals. No physiological counterparts are known.

The mechanism controlling the release of leucocytes into the circulation is little understood, but it would appear to be intact, if not overactive, in the aleukaemic forms of leukaemia (Whitby, 1951) and in the refractory anaemias associated with a paradoxically hyperplastic bone marrow (Whitby, 1952). The concept of hypersplenism and the rationale of its treatment with splenectomy implies, in fact, that the spleen has the power of regulating the release of all types of cells. Splenectomy, for any reason, may cause a considerable leucocytosis which may persist for years, but a leucocytosis does not occur in parabiotic animals unless the spleen is also removed from the second partner (Palmer *et al.*, 1951).

The interpretation of such results is, however, not always straightforward, as, for example, with the increase in circulating leucocytes which follows upon the injection of adrenaline. A critical examination of the cells in adrenaline leucocytosis shows no shift to the left in the Arneth count, and it would seem that the increase in cells is due to release of white cells from various sites of sequestration (Fig. 2) rather than to direct stimulation of or release from primary sites (Smith and Hayhoe, 1951). It may well be that the leucocytosis and leucopenia-producing factors of Menkin act also by controlling release of cells, as well as by stimulating a change in marrow activity.

Nucleic Acid Metabolism

Most, if not all, of the cells of the haemopoietic system have developmental processes in common, involving the synthesis and incorporation of substances less specific than the iron which is the essential constituent of haemoglobin, and which provides such an excellent marker for radioactive studies. Nevertheless, many of the highly differentiated cells have a unique composition, and all have intricate enzyme systems. A considerable speed in cell multiplication is obviously essential in order to replace daily wear and tear.

The vital chemistry of both red cells and leucocytes is concerned with nucleic acid metabolism. The nuclei and the cytoplasm of the young actively growing cells contain nucleic acids in high concentrations which are attached to proteins as nucleoproteins. These, in general, fall into two groups—the ribosenucleic acids with a sugar component of the pentose series, and desoxyribosenucleic acids with a sugar component of the desoxypentose series.

Cellular growth and active multiplication obviously depend upon the new formation of these fundamental substances within the cell, the nucleoproteins being the controlling factors, in that the energy necessary for synthesis is available within the molecular structure of nucleic acid.

Mitosis of marrow cells can proceed very rapidly when required, but it is not known whether a demand causes an increase in the number of cells undergoing mitosis, or shortens the time interval, or accelerates the process. Bone-marrow activity can be observed directly and the histological changes accurately described, and these in turn can be expressed roughly in terms of basic chemistry by cytochemical methods of staining.

The nucleoli and cytoplasm of blood cells contain ribosenucleic acids, and in the cytoplasm the ribosenucleic acids are found especially in the mitochondria, which are the site of enzymatic activities and probably serve as centres for protein synthesis.

The ribosenucleic acids of the nucleoli and cytoplasm appear to be concerned not only with the proliferation of young marrow cells but also with the synthesis of their characteristic cytoplasmic contents—namely, haemoglobin in the red-cell series and complex enzyme systems in the specific granules of the leucocytes (White, 1947); ribosenucleic acid diminishes as these specific substances appear (Thorell, 1947b).

The Feulgen reaction shows that the nuclei of early cells, particularly the chromatin and chromosomes, are rich in desoxyribosenucleic acid, especially during the period of active division of the cells, when it may well provide the energy necessary for the protein synthesis which takes place at this time.

The widely distributed enzyme alkaline phosphatase, which is found in normoblastic nuclei, is formed in large amount around the nucleus during active blood regeneration. The nucleus becomes infiltrated with the enzyme, after which pyknosis, fragmentation, or extrusion occurs. It is believed that alkaline phosphatase is intimately concerned with nuclear destruction. During active haemopoiesis, also, the magnesium content of the red cell is increased (Dahl, 1950), which is of interest since magnesium is a potent activator of the phosphatases.

A balanced production of the cells of the bone marrow clearly depends upon a carefully regulated chemical system, and since nucleic acids appear to govern cell division the differences in their concentration or availability may even determine the proportions of red and white cells in the blood. In certain pathological conditions there may be competition within a cell or between cells for substances which are essential for maintaining normal equilibrium.

The importance of these basic facts in practical haematology becomes clear as advances are made in knowledge concerning the factors essential for blood formation, as well as the manner in which these factors act. It is significant, for example, that thymine and thymidine have a haematological therapeutic action, whilst folic acid, citrovorum factor, and vitamin B_{12} may exert their essential activity as coenzymes for certain stages in the synthesis of nucleic acid from simple substances (Fig. 3).

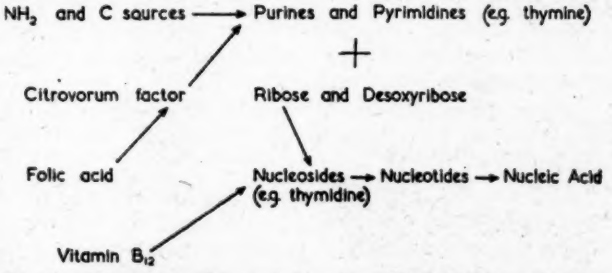

FIG. 3.—Scheme for the synthesis of nucleic acids from simpler substances, with suggested points of action of certain haemopoietic substances.

Abnormal Haemopoiesis

In some pathological processes the deviations from normal may be explained, or at least expressed, in terms of alteration in the normal rhythm. In other conditions the mode of action of an apparently specific material such as vitamin B_{12} or folic acid may be thought of as being due to the part it plays in the synthesis of essential cellular constituents from simpler substances, and especially in relation to nucleic acid metabolism (Fig. 3).

For example, Japa (1945) suggested that the essential abnormality in megaloblastic erythropoiesis was one involving nucleic acid metabolism preventing the proper development of nucleoli, thereby inhibiting the capacity for cell division and leading to a prolonged duration of mitosis, decreased frequency of division, earlier cessation of division, and consequent differentiation at an earlier genealogical stage.

In the marrow cells in pernicious anaemia the ribosenucleic acids of the cytoplasm and nucleolar apparatus do not disappear even when haemoglobin formation occurs (Thorell, 1947a). This is in contrast to what happens in

the normal subject, as well as in the haemorrhagic anaemias, even though haemoglobin synthesis in the latter is retarded by lack of iron. In leukaemia, leucocytes accumulate a high concentration of ribosenucleic acids in the cytoplasm and nucleoli which does not rapidly decline, as in the case of normal cells.

Desoxyribosenucleic acids are an important constituent of chromosomes, being apparently attached at specific loci in the polypeptide chain which goes to make up the chromosome fibre; the amount differs at the different phases of chromosome division, and is noticeably abnormal in certain pathological states.

Under normal conditions there is more desoxyribosenucleic acid in the chromosomes of the proerythroblast than the promyelocyte at the metaphase. In pernicious anaemia, however, the promyelocyte chromosomes contain very little desoxyribosenucleic acid, and this leads to incomplete spiralization; the proerythroblasts and early megaloblasts, on the other hand, show an excess which consequently leads to over-spiralization. Over-spiralized chromosomes are associated with irregular division, multipolar spindles, and chromatoid bridges at the anaphase. In short, it would seem that mitotic abnormalities are closely associated with different distributions of desoxyribosenucleic acid.

Conclusion

In this limited survey of some of the dynamic aspects of haemopoiesis I have naturally laid most emphasis on basic principles, some of which are now well established owing to the specific characteristics which the cells of the haemopoietic system possess. I have also paid some attention to the quantitative aspects of the subject and to some of the fallacies which may so easily intrude with hasty interpretation.

Simple quantitative aspects of haemopoiesis are indeed of such everyday application in clinical medicine that they are all too often accepted without critical analysis, without thought of possible alternative interpretation, or from a superficial viewpoint, to the neglect of fundamental principles.

Quantitative deductions cannot be accurate unless made upon unequivocal facts entirely free from ambiguity.

Leonard Huxley (1900) quotes Thomas Huxley, when writing to Charles Kingsley, as saying, "My business is to teach my aspirations to conform themselves to fact, not to try to make facts harmonize with my aspirations. Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly to wherever and to whatever abysses nature leads or you will learn nothing."

In no field of medicine is this more true than in haematology, which in its daily clinical application to the dynamics of haemopoiesis is largely quantitative and in which precise results require the most critical appraisal if they are to be properly and accurately assessed.

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ASSISTED CIRCULATION BY PUMP-OXYGENATOR DURING OPERATIVE DILATATION OF THE AORTIC VALVE IN MAN

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Interest in the clinical application of the various forms of pump-oxygenator (extracorporeal circulation or artificial heart–lung machine) is growing so rapidly, and the use of this type of apparatus in man has so seldom been followed by recovery, that it is customary for isolated examples of its use to be reported (Dennis *et al.*, 1951; Dogliotti, 1952; Gibbon, 1953; Dodrill *et al.*, 1953; Helmsworth *et al.*, 1953).

Three authors, Dogliotti (1952) in Turin, Gibbon (1953) in Philadelphia, and Dodrill *et al.* (1953) in Detroit, report survivors, and Helmsworth *et al.* (1952) have used an oxygenator for vein-to-vein perfusion in a case of fibrosis of the lung. The pump-oxygenator employed in the case here reported was that designed and developed by Melrose in the department of surgery of the Postgraduate Medical School. Melrose (1953a) has described the machine and Melrose *et al.* (1953b) have reported the animal experiments performed in the Buckston Browne Laboratories of the Royal College of Surgeons, which seemed to prove that the machine might be used with safety in man. The machine consists essentially of a rotating oxygenator and two rotary pumps. Its chief advantages are a high degree of efficiency in oxygenation (100 ml. of oxygen per litre of blood) and a low initial charge of blood.

The circumstances in which the machine might be used with profit in a clinical way have also been discussed (Aird, 1953), and the opinion was then expressed that the use of such a machine to by-pass heart and lung totally and to provide safely a dry heart for surgery was an aim not then immediately obtainable. We

now have evidence that with a machine of this kind the surgical approach to the interior of the heart and even to the mitral valve under vision may well be possible. We hope to approach this aim by using the pump-oxygenator as a form of assisted circulation during operation, gradually increasing the proportion of the total circulation for which it is responsible.

There are certain standard procedures in cardiac surgery whose performance at present carries the risk of a dangerous fall in the rate of flow in the coronary arteries and the development of a ventricular fibrillation or cessation of heart-beat which is sometimes irreversible. The maintenance of flow in the coronary arteries during such a procedure seems to lessen the risk of ventricular fibrillation, and its severity if it occurs. Notable among these procedures is an attempt to deal surgically with severe degrees of aortic stenosis. When a thoracic surgeon is faced during operation with a seriously low aortic pressure, decreased coronary flow, and loss of cardiac efficiency, he normally has recourse to cardiac massage, occlusion of the thoracic aorta, and gravity or pump transfusion of blood directly into the aorta above the clamp to maintain coronary and carotid flow, at least in part.

We decided that a more effective method of maintaining the mean aortic pressure at a level sufficient for an adequate coronary and carotid flow would be to apply the pump-oxygenator throughout operation in parallel with the patient's own heart and lungs as a form of assisted circulation which could function in emergency as a total replacement for heart and lungs if cardiac function should give rise to serious anxiety. The indication for its use should be, we feel, a patient seriously incapacitated by a form of cardiac disease amenable to surgery who would, without some form of assisted circulation, be refused operation as too great a risk. When a new apparatus is used in such cases and the patient does not survive it is extremely difficult to exonerate the apparatus from blame and to apportion responsibility fairly between the severity of the operation and the danger of the ancillary apparatus. Similarly, if the patient survives, it is difficult to say to what extent the machine was of benefit, and to disprove that the operation might perhaps have been performed without its use. Recovery does show, however, in what manner the apparatus may be used without doing the patient detectable harm.

Clinical Features

The patient with whom this report was concerned was 32 years of age. She had contracted rheumatic fever first at 13 years, with chorea thereafter, a second attack of rheumatic fever at 23 years, and progressive dyspnoea from 1948. Since 1949 there had been attacks of winter bronchitis, and in July, 1952, an attack of carditis with congestive heart failure. Consequent upon this there was anginal pain on the slightest exertion, and when the patient presented she had been bedridden for six to eight months. Before operation the heart was fibrillating slowly, the pulse was small and slow-rising, and there were clear signs of mitral incompetence and aortic stenosis.

The pre-operative electrocardiogram, the patient being on digitalis, showed slow auricular fibrillation. There was no evidence of ventricular hypertrophy or infarction.

It is perhaps clear even from so abridged a clinical description that an operative attempt to dilate the aortic valve would carry an extremely heavy risk of serious coronary inadequacy developing during operation unless some artificial method of maintaining a satisfactory aortic pressure were available. Before it was available, operation had in fact been refused on grounds of risk to life, and an attack of acute appendicitis had been treated conservatively (July, 1953) because of the high risk even of appendicectomy.

Operative Details

Operation (W. P. C.) was undertaken on December 9, 1953. After premedication with promethazine hydrochloride and pethidine, anaesthesia (Dr. John Beard) was induced at 2 p.m. with thiopentone and maintained with nitrous oxide, oxygen, and relaxants.

At 2.20 p.m. the superficial femoral artery and saphenous vein were exposed in the upper part of the right thigh. Seventy mg. (1 mg. per kg.) of heparin was then injected slowly. A 4-mm. (internal diameter) "polythene" catheter with multiple perforations was passed up the saphenous vein for a distance of 30 cm. so that its tip should lie in the inferior vena cava just above the diaphragm. On insertion of this catheter quite rapid bleeding occurred, through the perforations, before all the perforations lay within the vein. An obturator has now been devised for this catheter to prevent bleeding during its insertion and to be withdrawn when the venous catheter is in place. The venous catheter was held in place by a ligature around the vein, the distal vein being ligated. The artery was then controlled by two tapes and opened by a transverse incision. The arterial catheter, 2.5 mm. in internal diameter, was then passed up the femoral artery to a distance of 45 cm. so that its tip should lie within the arch of the aorta. A tape around the proximal artery and catheter was kept tight as a temporary ligature by an artery forceps. The distal artery was controlled by a bulldog clamp. Both catheters were in place at 2.40 p.m. and at 2.43 the pump was started at a rate of 500 ml. a minute; the pulse was not palpable at the wrist at this time. The chest was entered through a postero-lateral incision in the fifth intercostal space. Bleeding was not excessive, though the clotting-time was 30 minutes. At 3.10 the pericardium was opened to reveal a moderate excess of pericardial fluid and a very large tense left ventricle. The left atrium was aneurysmal and exhibited well-marked systolic pulsation. A systolic thrill was felt on the atrial wall below the inferior pulmonary vein, a coarse systolic thrill on the ascending aorta. Aortic valve closure was not palpable. The heart rate was now 84 and the radial pulse was just palpable and irregular. The pump rate was increased to 600 ml. a minute.

At 3.16 p.m. the heart was opened through the auricular appendage to reveal free mitral incompetence through a circular valve opening approximately 3 cm. in diameter. There was no stenosis of the mitral valve.

At 3.23 p.m. left ventricular cardiotomy was performed, using a purse-string suture and Rumel's tourniquet. A guide wire was inserted through the ventricle and aortic valve into the aorta. The valve was fully dilated on three separate occasions with the triradiate Bailey dilator. No noticeable disturbance of heart rate or rhythm or any alteration in the force of the beat was detectable during these manœuvres. The heart rate was 50–60 with periodic extra beats. The pump rate throughout this manœuvre was maintained at 800 ml. a minute. At 3.30, after the dilatation, the aortic systolic thrill was noticeably less. Re-examination of the mitral valve did not reveal any noticeable alteration in the regurgitant flow of blood through the valve. At 4 p.m. both cardiotomy wounds were closed with interrupted sutures and the pericardium was loosely stitched. The blood pressure in the arm was now 100 mm. Hg and the radial pulse was palpable. The rate of extracorporeal circulation was slowed progressively from 800 ml. to 500 ml. during closure of the cardiotomy incision and was decreased still further to reach 300 ml. a minute at 4.20, when it was discontinued, after the pump had been in operation for 97 minutes.

The chest was kept open for three-quarters of an hour after completion of the cardiotomy until the rather persistent oozing, noticed towards the end of the operation,

had ceased. At 5 p.m. the catheters were removed from the saphenous vein, which was ligated, and from the femoral artery, which was repaired with 00000 arterial silk. The groin incision was closed in layers, and 70 mg. of protamine sulphate was given intravenously as a 0.01% solution in isotonic saline. The clotting-time after operation was 6–8 minutes. The estimated blood loss during operation was 6 pints (3.4 litres); and 7¼ pints (4.3 litres) of blood, 4 pints (2.3 litres) of them freshly drawn, were given by transfusion. The pharyngeal temperature was 36.4° C. at the end of operation.

The mixed venous blood during the running of the machine showed an oxygen saturation of 78 to 76%, and a carbon dioxide content of 47–45 volumes %.

The serum potassium arose from a pre-operative level of 3.7 mEq/l. to a maximum of 6 mEq/l. during operation, falling again to 4 mEq/l. on the evening of operation.

At 6 p.m. the patient was returned to the ward already conscious; at 6.5 she asked what time it was.

Electrocardiographic Studies During Operation

A continuous E.C.G. tracing was run during the operation, and some 40 feet (12 metres) of this was recorded. We are indebted to Dr. J. F. Goodwin and Dr. L. G. Davies for its interpretation. At the beginning of the operation the electrocardiogram showed, as it did before operation, slow auricular fibrillation. This continued until 3.16 p.m., when during exploration of the left atrium the E.C.G. showed occasional ventricular ectopic beats from multiple foci, and auricular fibrillation. At 3.23, during dilatation of the aortic valve, there were various multifocal ventricular ectopic beats, some T-wave inversion following normal QRS complexes, and auricular fibrillation. At 3.30, following aortic-valve dilatation, occasional ectopic beats were seen. The QRS complex lost its Q and developed a deep S wave, with T still upright and taller than before. This was thought to be due either to a clockwise rotation around the long axis of the heart or perhaps to a diminution of left ventricular strain. Auricular fibrillation was still present. At 4 p.m. auricular fibrillation was still present, but there were no ectopic beats and the T waves had increased in height. No further change in the E.C.G. occurred while the chest was closed. At 10 p.m. slow auricular fibrillation was present as before operation, and the QRST complex had returned to normal.

Post-operative Course

On the evening of operation there was slight cyanosis of the lips, but the patient was fully conscious and in possession of all faculties two hours after operation. Cyanosis faded within four hours of the end of the operation.

Subsequent progress was uneventful, only 26 oz. (740 ml.) draining from the chest, but there was extensive ecchymosis of the chest wall round the thoracotomy incision and around the stab drain. Clinically the aortic systolic murmur is now softer and the patient has not experienced anginal pain such as was her chief complaint before operation. Convalescence has proceeded satisfactorily apart from a thrombophlebitis of the catheterized saphenous vein. Pulses did not return in the ankle of the limb whose femoral artery had been catheterized, but the limb remained warm and identical in appearance and temperature with its fellow of the opposite side. An improvement in exercise tolerance permits the climbing of 48 steps without undue distress. Previously completely bedridden, the patient can now walk many hundreds of yards. She has returned home and her exercise tolerance still improves daily.

Bleeding

Dr. S. J. Baker, of the department of haematology, has been our adviser on this subject, and has provided this report.

All workers in the field of extracorporeal circulation experience trouble with haemorrhage, both in experimental animals and in human subjects. In this patient excessive bleeding occurred especially towards the end of the operation, even after the administration of adequate amounts of protamine to neutralize the heparin. This bleeding is explicable, at least in part, by the development of a thrombocytopenia. The platelet count (direct method) fell from a pre-operative level of 217,000 to 44,000 per c.mm. in the first half-hour after application of the machine. It remained at this level until several hours after the completion of the operation. Over the next eight days it gradually returned to the pre-operative level.

Immediately after operation the one-stage "prothrombin time" was normal, so factors V and VII were apparently still present in adequate amounts. Antihaemophilic globulin and Christmas factor were not tested for in this case, and it is possible that these may have been reduced.

There are three factors which may produce a deficiency of coagulation components: (1) the operation itself—coagulation factors, especially platelets, are sometimes reduced during major surgical procedures; (2) the "dilution" effect of replacing a considerable proportion of the patient's blood by stored "bank" blood, which contains no platelets and will probably be deficient in antihaemophilic globulin and factor V, to an extent depending on the length of storage; and (3) the machine, which, although lined throughout by silicone, causes marked loss of platelets presumably by adhesion to foreign surfaces and/or by mechanical destruction.

The most effective available method of correcting the thrombocytopenia in a patient at the end of a procedure such as this would appear to be the transfusion, or replacement transfusion, of a substantial quantity of platelet-rich blood freshly drawn into siliconed apparatus, or the use of a direct platelet transfusion. Bell and others (Bell, 1953; 1954) in Gibbon's unit have made an extensive survey of coagulation disorders arising after massive simple transfusion, and also during the course of extracorporeal circulations. Their work suggests that, apart from the thrombocytopenia, the "dilution" effects could be prevented by the use of blood not more than 48–72 hours old; but this may be difficult to achieve.

Conclusions

The pump-oxygenator previously described has been shown at least not to be productive of serious immediate toxic effects, and no delayed effects can be predicted on theoretical grounds.

It is our impression that the machine has been helpful when used to assist the circulation of a human patient throughout a severe cardiac operation which would not have been attempted without some kind of artificial help. Throughout the operation no anxiety was felt concerning the coronary circulation, as measured by the visible contraction of the ventricle and the electrocardiogram. Previous experience without the use of the machine has shown that even less severe aortic dilatations performed in patients less debilitated have been accompanied sometimes by irreversible disturbances of cardiac rhythm. There was never any threat in this case of cardiac cessation or ventricular fibrillation during two explorations of the left atrium and mitral valve, and three separate forcible dilatations of the aortic valve.

We have previously stated that the chief therapeutic use we saw immediately for this machine was its application to extreme cardiological emergencies, and we propose to apply it to this purpose, for it is capable not only of increasing oxygenation but of reducing the blood carbon dioxide to any desired level, so avoiding the dangers of present methods of oxygen therapy in heart failure. We consider now, however, that this machine may also be used to open the way gradually towards the ultimate aim of a pump-oxygenator for routine total replacement at surgical operations. Rare congenital defects in infants are susceptible to open repair under vision with the assistance of cooling. In adults, selected cases of aortic stenosis may be treated

with every chance of improvement without the use either of cooling or of the extracorporeal circulation, but the most important aim of modern surgery is the direct correction under vision of the adult mitral valve, and this can be attained only by some form of assisted circulation.

It may be that one way of progressing towards this aim of a dry adult heart for the routine performance of surgery on its interior may be the use of an assisted circulation to take over in successive cases more and more of the circulation.

Experience will show what amount of aortic flow per minute is required for the maintenance of an adequate coronary and carotid circulation, but previous experience with pressure perfusion of the clamped aorta in emergency, by quantities of blood per minute small in proportion to the output of the pump, suggests that the necessary flow may not in fact be particularly high. On this occasion a flow of 500 to 800 ml. was maintained for a total period of 97 minutes, and it might be estimated that in that time there was a total flow of 70 litres through the machine. Alternatively, it might be said that the patient's total volume of circulating blood passed through the machine about 15 times, or that, for 97 minutes, the machine was responsible for 20 to 30% of the total cardiac output.

Bleeding during and after the operation is the most serious problem which we have to face, but we prefer the risk of bleeding as we experienced it in this patient to the still greater risk of clotting around the tubes of the machine at some critical stage of operation during which the patient's life might depend upon the efficiency of the artificial circulation. It seems reasonably certain that the bleeding we experienced was due in the main to platelet loss, though the effect of operation, transfusion of foreign blood, and the machine on clotting function is highly complex, and other factors certainly operate too. Methods are being developed for the collection of fresh blood rich in platelets; even fresh blood, drawn by routine methods, loses a high proportion of platelets in collection.

All the data collected concerning the effect of the machine have not been presented here—much of the material cannot be fully analysed until a series of cases is available for study. The management of collecting devices and the drill for the timing of samples require a large team of medical and technical staff, and the arrangements and control of apparatus, especially collecting apparatus in an operating-room already occupied by a complex surgical team, have been the subject of prolonged study and experiment.

We wish to acknowledge our indebtedness to many colleagues and assistants who have been concerned in this work and in the management of the case here reported. To the cardiologists at Hammersmith Hospital, including Dr. J. F. Goodwin and Dr. R. I. S. Bayliss, we owe a great deal of day-to-day advice and the pre-operative investigation and management of patients who are considered for this and other forms of surgery. We are indebted for help and advice in our electrocardiographic studies to Dr. J. F. Goodwin and Dr. L. G. Davies. Dr. S. J. Baker, of the department of haematology, has given much time and thought to our problems of coagulation and haemorrhage. Dr. John Beard, anaesthetist for thoracic surgery in the Postgraduate Medical School and Hammersmith Hospital, has been a most important member of the operative team, and has collaborated most helpfully. Mr. Ralph Shackman and the staff of the Surgical Research Laboratories have given us constant help, and Mr. Gerald Rainbow and Miss Eva Bottoms particularly have been unwearied in the maintenance of the machine. With New Electrical Products Ltd. we have explored now for a long period, and very happily, the technique of liaison between surgical and technological research; and Mr. J. Brown of that company has not only devoted endless time and skill to the original construction of the machine but has attended and studied its performance in the operating theatre. A second phase of this prototype apparatus embodying improvements which the function of this machine has suggested is now under construction; the cost of its development is being borne by a grant from the Nuffield Foundation. We have had assistance from the National Research Development Corporation in our plans for the machine's development.

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INSULIN RESISTANCE FOLLOWING HYPOTHALAMIC LESIONS AND REMOVAL OF THE ADRENAL MEDULLA

BY

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It has long been thought that insulin-resistant diabetes might be associated with the presence of an insulin antagonist (Himsworth and Kerr, 1940). Resistance to insulin has been shown to develop in intact animals after the injection of purified growth hormone (Young, 1950) and of cortisone (Campbell *et al.*, 1950) over periods of some days. The work of Bornstein and Park (1953) has shown that neither of these hormones is an insulin antagonist, but that both are necessary for the development in the intact animal of the insulin antagonism found in alloxan-diabetic rats. Bornstein (1953) found that the insulin antagonism was confined to a specific lipoprotein fraction of the serum of such rats. The serum from a human subject rendered hypoglycaemic by a large dose of insulin also exhibited insulin antagonism, while that from a normal human subject and from normal rats possessed no such activity.

Section of those pathways from the hypothalamus to the brain stem which mediate autonomic function produced no change in insulin sensitivity (Beattie and Chambers, 1953a), but when the adrenal medulla was removed from these rats they developed marked resistance to insulin. These experiments are described below.

Material and Methods

Male albino rats of a single strain and weighing between 200 and 250 g. at the start of the experiment were used. For five weeks before the experiments began they were kept at a constant environmental temperature of 29.5° C. Rats of the series 1 experiments were kept at this temperature throughout the experimental period. Rats of the series 2 experiments were kept at 29.5° C. until day 12 of the experiment, when they were transferred to a cooler environment with a mean temperature of 18° C.

The rats of each series were divided into four groups. Group A rats were unoperated controls. Group B rats had brain lesions inflicted on day 0. The adrenal medullary tissue was removed from the group C rats on day 7. Group D rats had brain lesions made on day 0 and the adrenal medullary tissue was removed on day 7. All rats were killed on day 21.

Each group of rats in series 1 was divided into four subgroups. The first subgroup was used to obtain resting blood-glucose and resting liver-glycogen values. The second subgroup was given an intraperitoneal (I.P.) injection of insulin (1 unit per kg. body weight) on day 21. Blood-

glucose concentrations were determined on blood samples taken before and 30 minutes after the injection. The third subgroup received an I.P. injection of glucose (1 mg. per g. body weight) on day 21. Blood-glucose concentrations were determined as in the previous group. Samples of muscle were taken before and 30 minutes after the injection, and a sample of liver also 30 minutes after the injection. These tissue samples were used to determine the glycogen content. The fourth subgroup received an injection of glucose and insulin at the above dose levels and by the same route. Samples of blood, muscle, and liver were taken as in the third subgroup. The rats of series 2 were used only to determine resting blood-glucose and liver-glycogen values and the response of the blood glucose to an injection of insulin. The insulin used in all the experiments came from the same batch and had been assayed for glucagon content.

The site of the brain lesions and the method of producing them have been described already (Beattie and Chambers, 1953b). The adrenal medulla was removed by incising the cortex and expressing the medulla by gentle pressure on the cortex. At the end of the experiment the glands were fixed and sectioned to confirm that no remnant of medullary tissue had been left within the gland.

The procedures at the end of the experiment were :

1. Food was withdrawn at 5 p.m. on day 20 but ample water provided.

2. Between 10 a.m. and 12 noon on day 21 the rats were anaesthetized by an I.P. injection of pentobarbitone sodium (40 mg. per kg. body weight).

3. When anaesthetized a blood sample (0.2 ml.) was withdrawn from the heart. The left gastrocnemius muscle was exposed, ligated near its origin, and a sample (approximately 0.4 g.) removed, avoiding any obvious tendinous tissue. After weighing on a torsion balance, the sample was dropped into 4 ml. of a hot (100° C.) solution of potassium hydroxide (30% w/v).

4. Immediately after removal of the muscle sample the injection of insulin, glucose, or glucose with insulin was given. The total volume of fluid injected did not exceed 0.6 ml. per 100 g. body weight.

5. Precisely 30 minutes after the injection a second blood sample was taken from the heart, and after its removal a sample of muscle was removed from the right gastrocnemius muscle and treated as before.

6. The abdominal cavity was opened and a sample of liver (approximately 0.4 g.) taken from the left lateral lobe and treated in the same way as the muscle samples.

Blood samples were deproteinized by the barium–zinc procedure and the glucose content was determined by the method of Nelson (1944). After the samples of muscle and liver had dissolved, the tubes were cooled and the glycogen precipitated by adding 7.2 ml. of absolute alcohol. After centrifuging, the supernatant fluid was discarded, and the precipitate dried and then dissolved in 10 ml. of distilled water. Glycogen was determined (as glucose) by the anthrone method of Seifter *et al.* (1950). The glycogen content of liver and muscle was expressed as grammes of glucose per 100 g. wet tissue.

Results

Effect of Insulin on Blood-glucose Level.—The mean resting blood-glucose concentrations were considerably lower in group D rats of both series than those of the other groups. Rats of group D in both series failed to show a hypoglycaemic response after the injection of insulin (Table I).

Muscle-glycogen Content.—The glycogen content of muscle was determined only on series 1 rats. Rats with brain lesions only (group B) had a resting content of glycogen which was not significantly different from that in the control group. After removal of the adrenal medulla (group C) the resting level of glycogen was lower in one set of experiments and equal to that of the control rats in another set. Group D rats had a resting content significantly lower than that of the control group (Tables II and III). After the injection of glucose the glycogen content of muscle rose by almost the same amount in groups A, B, and C, but that of group D remained unchanged (Table II). When insulin and glucose were given the glycogen content rose again in groups A, B, and C, but not in group D. The blood-glucose levels fell in groups A, B, and C, but rose in group D by the same amount as it had when glucose alone was given (Table III).

Liver Glycogen.—The resting glycogen content of the liver in series 1 rats was not significantly different in groups A and B. The mean content in group C was significantly lower than that of groups A and B. Rats of group D had

TABLE I.—*Changes in Blood-glucose Concentration Following Insulin Injection*

Group	Operation	Series 1 Environmental temp. 29·5° C. Blood Glucose, mg./100 ml. ±S.E. No. of Rats	Resting Level	30 min. after Insulin	Diff.	Series 2 Environmental temp. 18° C. Blood Glucose, mg./100 ml. ±S.E. No. of Rats	Resting Level	30 min. after Insulin	Diff.
A	Control	6	119±3·6	71±4·4	−48	8	96±5·9	64±4·9	−32
B	Lesions	5	100±5·0	63±3·3	−37	11	98±4·0	46±3·8	−52
C	Adrenal medulla removed	10	111±5·2	71±5·5	−40	10	115±5·8	58±3·3	−57
D	Lesions and adrenal medulla removed	7	60±1·6	69±9·2	+9	7	73±4·1	89±8·2	+16

Insulin dose, 1 unit per kg. body weight given intraperitoneally.

TABLE II.—*Changes in Blood-glucose Concentration and Glycogen Content of Muscle and Liver After Injection of Glucose in Series 1*

Group	Operation	Blood Glucose Mean±S.E. mg./100 ml. Blood No. of Rats	Resting Level	30 min. after Glucose	Muscle Glycogen Mean±S.E. g./100 g. Resting Level	30 min. after Glucose	Liver Glycogen Mean±S.E. g./100 g. After Glucose
A	Control	7	104±6·5	156±7·2	0·635 ±0·008	0·691 ±0·010	1·346±0·107 (0·962)
B	Lesions	4	110±5·9	145±5·7	0·652 ±0·009	0·684 ±0·006	1·436±0·129 (1·178)
C	Adrenal medulla removed	4	102±5·1	162±7·9	0·515 ±0·008	0·541 ±0·006	0·840±0·064 (0·658)
D	Lesions and adrenal medulla removed	4	84±4·7	104±4·9	0·468 ±0·004	0·458 ±0·007	0·213±0·024 (0·120)

Dose of glucose, 1 mg. per g. body weight given intraperitoneally. Values in parentheses under the mean glycogen content of liver are mean resting values from Table IV.

TABLE III.—*Changes in Blood-glucose Concentration and Glycogen Content of Muscle and Liver After Injection of Glucose and Insulin in Series 1*

Group	Operation	Blood Glucose Mean±S.E. mg./100 ml. blood No. of Rats	Resting Level	30 min. After Glucose and Insulin	Muscle Glycogen Mean ±S.E. g./100 g. Resting Level	30 min. After Glucose and Insulin	Liver Glycogen Mean±S.E. g./100 g. After Glucose and Insulin
A	Control	7	109±5·6	92±5·2	0·736 ±0·011	0·750 ±0·009	1·463±0·098 (0·962)
B	Lesions	4	100±4·1	79±3·8	0·687 ±0·007	0·705 ±0·010	1·397±0·077 (1·178)
C	Adrenal medulla removed	3	106±5·0	84±4·8	0·690 ±0·011	0·736 ±0·009	0·948±0·089 (0·658)
D	Lesions and adrenal medulla removed	4	104±3·9	124±5·2	0·519 ±0·008	0·497 ±0·011	0·248±0·027 (0·120)

Dose of glucose, 1 mg. per g. body weight. Dose of insulin 1 unit per kg. body weight. Values in parentheses under the mean glycogen content of liver are mean resting values from Table IV.

a very low content equal to about 15% of that in the control group. After exposure to cold conditions for nine days all liver glycogen values were markedly reduced. Group C rats again had a lower mean content than the control group and those of group D an extremely small amount (Table IV).

TABLE IV.—*Resting Glycogen Content of the Liver- and Blood-glucose Levels*

Group	Operation	No. of Rats	Series 1 Environmental Temp. 29·5° C.		Series 2 Environmental Temp. 18° C.	
			Blood Glucose Mean ±S.E. mg./100 ml.	Liver Glycogen Mean ±S.E. g./100 g.	Blood Glucose Mean ±S.E. mg./100 ml.	Liver Glycogen Mean ±S.E. g./100 g.
A	Control	8	111±5·3	0·962±0·042	96±5·9	0·073 ±0·010
B	Lesions	8	103±4·7	1·178±0·061	98±4·0	0·073 ±0·008
C	Adrenal medulla removed	8	106±5·7	0·658±0·037	115±5·8	0·045 ±0·005
D	Lesions and adrenal medulla removed	8	78±4·9	0·120±0·008	73±4·1	0·011 ±0·004

All determinations were made on day 21 of the experiment. Series 2 rats had been exposed for 9 days to an environmental temperature of 18° C. from day 12 to day 21.

Body-weight Changes.—The differences between the mean weight at the start of the experiment and that on day 21 are given in Table V. Series 1 rats all showed an increase in weight which was not significantly different between

TABLE V.—*Changes in Body Weight During the Experimental Period*

Group	Operation	Series 1 Environmental Temp. 29·5° C.		Series 2 Environmental Temp. 18° C.	
		No. of Rats	Mean Change of Weight ±S.E. g.	No. of Rats	Mean Change of Weight ±S.E. g.
A	Control	28	+24±7·6	16	+20±5·2
B	Lesions	21	+20±5·8	19	1± 4·2
C	Adrenal medulla removed	25	+22±8·6	18	+5±9·6
D	Lesions and adrenal medulla removed	23	+13±11·7	15	−7±10·1

The change in body weight is the difference between the weights of rats on day 0 and those on day 21.

groups. The control rats of series 2 had the same overall weight increase as the corresponding group in series 1. Rats of groups B and C maintained their starting weight, and those of group D showed a slight fall below the weight at the beginning of the experiment.

Discussion

Rats of series 1 (kept at 29.5° C.), which had brain lesions and were without any adrenal medullary tissue, showed no hypoglycaemic response after the injection of insulin and were unable to increase the glycogen content of muscle either in the presence of a slight hyperglycaemia following the injection of glucose or when insulin was given with glucose. Rats with either no adrenal medullary tissue or with brain lesions responded to these various injections of insulin, glucose, and insulin with glucose in the same way and to the same degree as the control rats. The glycogen content of the liver in rats on whom both operations had been done was much reduced. These findings suggest that an insulin antagonist was present in the rats with brain lesions and without adrenal medullary tissue, and that this antagonist was probably inhibiting the hexokinase system.

Bornstein and Park (1953) found that the insulin antagonism shown by the serum of alloxan-diabetic rats was reversible by insulin in a concentration of 0.1 unit per ml. in the medium in which the isolated diaphragm from a normal rat was suspended. If the test muscle was taken from an alloxan-diabetic rat and suspended in serum from such a rat then insulin in this concentration failed to produce complete reversal of the insulin antagonism. Krahl (1951) had already pointed out that reversal of insulin antagonism was possible, provided there was enough insulin available. In the present experiments insulin was given in a dose of 1 unit per kg. body weight. Assuming that all the insulin was distributed over the extracellular fluid of the rat, and that this space forms about 28% of the weight of the rat, then the maximum concentration of insulin in the fluid bathing the muscle cells could not have exceeded 0.1 unit per 28 ml. if the insulin were evenly distributed throughout the space. It was probably much less. Rats of groups A, B, and C responded to this low concentration of insulin by increasing the muscle glycogen content, but the rats of group D did not. It would appear, therefore, that the insulin resistance exhibited by rats of group D would require an extremely high concentration of insulin for its reversal.

Bornstein and Park (1953) demonstrated that the presence of both growth hormone and cortisone was essential for the development of insulin antagonism in the serum of the hypophysectomized and alloxan-diabetic rat. If either or both hormones were added to normal serum no insulin antagonism was developed in that serum. If the insulin antagonism found in the rats of group D was of the same type as that found by Bornstein and Park, it would require both hormones for its development. The data in Table V leave no doubt that rats kept at 29.5° C. with brain lesions and with no adrenal medulla were able to increase their weights over a period of 21 days. It may be presumed, therefore, that these rats produced growth hormone at a rate at least as great as that of normal rats. These rats, too, showed no evidence of adrenal cortical deficiency, and normal cortical tissue was found in all the adrenal glands examined. It is reasonable to infer that these rats were producing, in quantities at least sufficient for normal existence, both corticotrophin (A.C.T.H.) and adrenal cortical steroids. Thus there is reason to believe that the two hormones necessary for the production of insulin antagonist of the Bornstein and Park type were present in rats of group D.

The mere differences in body weights recorded on day 0 and on day 21 do not give a true picture of the pattern of weight change. When brain lesions of the type inflicted in the present experiments are made there is a loss in body weight of about 20 g. during the first four days after the operation. This loss is made good by the end of the ninth day (Beattie and Chambers, 1953b). Removal of the adrenal medulla is followed by weight loss of about the same amount and is repaired in about the same time. Rats in group D thus repaired a total post-operative weight loss of about 40 g., and in addition increased their body weight by 13 g. above that on day 0. The true increment of weight in group D rats during 21 days was thus about 53 g., as compared with a weight increase in control rats of about 24 g.

Rats exposed to cool conditions (18° C.) react to these conditions by increasing heat production. Normal rats increased their oxygen consumption by 8%, those with brain lesions by 13.5%, rats without adrenal medulla by 15%, and rats without adrenal medulla and with brain lesions by 22% (Beattie and Chambers, 1953c). Thus after single operations (groups B and C) a weight loss of about 20 g. was repaired in spite of an increased oxygen consumption of 13.5–15%. The rats of group D regained almost all the weight loss after the two operations in spite of a rise in oxygen consumption of 22%. It would therefore not be unreasonable to presume that the rate of growth-hormone production, and probably also that of adrenal cortical steroids in the group D rats, was greater than that in normal rats under the same environmental conditions.

The exact role of the hypothalamus in the control of production of growth hormone and of corticotrophin (A.C.T.H.) is still obscure. Information derived from the effects of lesions in experimental animals and from the effects of tumours in man is equivocal. For example, Spirtos (1954) found that moderate-sized lesions of the hypothalamus (area unspecified) were followed by increased insulin sensitivity which could be countered by injections of growth hormone. Paton and Petch (1954) reported hyperglycaemia, a diabetic type of glucose-tolerance curve, and reduced sensitivity to insulin in a human subject in whom a brain tumour involving the hypothalamus (area unspecified) was discovered at necropsy. It would be valueless to attempt to explain the present findings in terms of hypothalamic function when such a conflict of evidence exists.

The interest of the present experiments lies in the fact that insulin resistance was produced in rats without destruction of pancreatic islet tissue and without the continued injection of hormones. Moreover, no direct damage was caused to the cell masses of the hypothalamus by the division of the fibre tracts leading from the hypothalamus to the brain stem. Late chromolytic changes were seen in certain cell masses which could with certainty be attributed to the section of the efferent fibres from them. Neither of the two operative procedures used in the production of insulin resistance had any demonstrable effect on insulin sensitivity. The insulin resistance which followed when both operations were done on the same rats was present 21 days after infliction of the brain lesions and 14 days after removal of the adrenal medulla. It is therefore improbable that the insulin resistance could be due to some irritative action set up by the operative procedures.

If the insulin resistance induced in these rats were due to the presence of an insulin antagonist—and the evidence is consistent with this assumption—then the possibility that insulin-resistant diabetes might arise from a cause or causes which do not involve primarily either the pancreas or the pituitary gland must receive serious consideration.

Summary

After section of the pathways from the hypothalamus to the brain stem and removal of the adrenal medulla, rats kept at an environmental temperature of 29.5° C. showed no fall in the blood-glucose level 30 minutes after the injection of insulin in a dose of 1 unit per kg. body weight. Removal of the adrenal medulla alone or section of the hypothalamic pathways produced no change in insulin sensitivity.

The resting content of glycogen in muscle (gastrocnemius) was significantly lower than normal in rats with the hypothalamic lesions and without adrenal medullary tissue. The glycogen content did not rise after the injection of glucose (1 mg. per g. body weight) or after the simultaneous injection of glucose and insulin. The glycogen content of the liver was markedly reduced (15% of normal) in the resting state. When such rats were exposed to cold for nine days they still displayed no hypoglycaemic response to the injection of insulin. The glycogen content of the liver in the resting state was reduced to 11 mg. per 100 g. of liver.

The experimental data suggest that the insulin resistance found in these rats was due to the presence of an insulin antagonist.

It is a pleasure to thank those who have made this work possible. Dr. Honor B. Fell placed laboratory facilities at my disposal, Mr. F. G. Moore and Mr. H. N. Smith made it possible to acquire most of the necessary equipment, and the Medical Research Council met part of the cost of technical assistance. I am indebted to Mr. R. D. Chambers for carrying out the major portion of the technical work.

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THE OCCURRENCE OF ELECTROCORTIN IN HUMAN URINE

BY

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The discovery by Grundy, Simpson, and Tait (1952) of a new hormone, called electrocortin,* which has the ability to increase both sodium retention and potassium excretion by the kidney, must inevitably give a new impetus to the study of the many conditions associated with sodium retention in man.

In recent years several workers have found evidence of the occurrence in certain human urines of a substance having the power to increase sodium retention by the kidney; but careful analysis of extracts of such urines by modern chromatographic methods has failed to reveal any evidence of the presence of deoxycortone, the only steroid hitherto known to possess such sodium-retaining properties in marked degree. It now seems likely that the sodium-retaining effects observed by earlier investigators were due to the presence in the extracts of this new hormone, electrocortin.

Most of the original observations suggesting the presence of a sodium-retaining principle in urine were made by Deming and Luetscher (1950). Using a method of bioassay on young adrenalectomized rats, they found that chloroform extracts of some human urines had the power, when injected, of reducing sodium excretion by the kidney. Under the conditions of their test deoxycortone acetate in doses of 5 to 25 μg. per rat had a similar effect, but larger doses of extract did not give greater sodium retention. In their earlier experiments evidence for the existence of a sodium-retaining substance in normal urine was equivocal, but a significant degree of activity was found in extracts of the urine of five out of eight patients with cardiac failure. In one patient with nephrosis a high titre of activity was also found. An extension of these observations was reported by Luetscher *et al.* (1952), who then found that the titre of sodium-retaining substance was high in the oedematous stage but fell to normal levels after diuresis with elimination of the oedema.

In 1953 Singer and Venning also found some evidence of sodium-retaining activity in extracts of nephrotic urine, and McCall and Singer (1953) found a sodium-retaining substance in eight out of nine nephrotic chil-

*The chemical formula of electrocortin has just been published by Simpson, Tait, Wettstein, *et al.* (*Experientia*, 1954, **10**, 132). It proves to be a steroid similar to corticosterone, but with an aldehyde grouping on C 18.

dren when they were gaining weight, though it was present in only one out of six when weight was stationary and the patients were no longer retaining sodium.

Chart and Shipley (1953) have claimed to detect a sodium-retaining factor excreted by normal adult males, the daily amount being equivalent in activity to 40 to 80 μg. of deoxycortone. They found that patients with hepatic cirrhosis and ascites showed a high excretion equivalent to as much as 3,162 μg. daily, although when ascites was absent excretion was normal. These workers also obtained some evidence that the active principle differed from deoxycortone itself, for they noted that it entered the aqueous phase when partitioned between benzene and water, whereas deoxycortone itself tends to enter the benzene phase freely. They suggested that it is probably associated with the so-called amorphous fraction of the adrenal cortical extract.

In 1951 Zaffaroni and Burton made a careful analysis of the steroids in adrenal cortical extract, employing their own particularly suitable and sensitive methods of paper-partition chromatography. They were able to find small amounts of deoxycortone in aqueous extracts of adrenal cortex, but could not find any trace of the hormone in chloroform extracts of human urine made at *p*H 1. Since a large part of the cortisone and hydrocortisone (compound F) content of such urines is extracted by chloroform at this *p*H it seems likely that any deoxycortone present would also be extracted in this way.

In 1952 Grundy *et al.* first published their evidence for the existence of a hitherto unrecognized hormone in the adrenal cortex causing sodium retention by the kidney. They were able to show that the new hormone was quite distinct from deoxycortone, for there was a great difference in the rates at which the two substances ran on paper chromatograms. In the toluene/propyleneglycol system of Burton, Zaffaroni, and Keutmann (1951) it ran at a rate almost exactly the same as cortisone, whereas deoxycortone ran very much faster. The activity in the cortisohe zone was much greater than could be accounted for by the activity of the small amount of cortisone actually present there.

Simpson and Tait (1953) have reviewed the further intensive work they have done on this new hormone. They find that it is a reducing steroid having from 50 to 90 times the activity of deoxycortone on an equimolecular basis. The culmination of this work has been the isolation of the new hormone in the form of crystals by Simpson, Tait, Wettstein *et al.* (1953). Desaulles *et al.* (1953) have tested this purified preparation and found it to be 25 times as potent as deoxycortone on sodium retention and five times as active in increasing potassium excretion. An independent account of the properties and isolation of this hormone has been published by Mattox *et al.* (1953).

In the work presented here we have employed the assay procedure developed by Simpson and Tait for electrocortin activity to look for this hormone in human urine extracts. Our results suggest the presence of a small amount in normal urines. In addition a patient has been found who was shown on several occasions to be excreting large quantities of a substance having the special properties of electrocortin but who showed no evidence of sodium retention.

Methods

The rats used in these experiments were young of an albino strain bred in the department and weighing 60 to 80 g. Bilateral adrenalectomy was performed by the dorsal approach under ether anaesthesia. Only animals whose adrenals were removed unbroken were used. After operation the animals were fed a stock diet of "research" rat cubes and drank unrestricted 1% saline solution. Assays were carried out on the fourth day after operation. Each group of test animals consisted of five to seven rats and a control group of the same size was used on each day of testing. In preliminary experiments it was observed that variations between control groups from one week to another were greater than the differences between males and females. For this reason both male and female rats have been used in these experiments, though all animals in any one assay were of the same sex. Control and test animals were mixed in the cages to avoid variations due to the order in which the animals were handled.

In the earlier experiments survival time after withdrawal of saline was determined as evidence of completeness of adrenalectomy, but survival, implying an incomplete adrenalectomy, was so rarely observed that this was finally abandoned as a routine. The rats were allowed to continue drinking saline until the morning of the test day.

For each test four groups of five to seven rats were taken. The first group served as controls, the second group all received 10 μg. of deoxycortone, and the third and fourth groups were injected with different quantities of the extract to be tested. All injections were made up to a volume of 0.1 ml., the solvent being 20% ethanol in water. The control group received solvent alone. The injections were made at about 10 a.m. on the morning of the test. One hour later the bladders of all rats were emptied by suprapubic pressure combined with a light inhalation of ether. After this, a subcutaneous injection of 1 ml. of a mixture containing 73 μg. of Na^{24} and 295 μg. of K^{42} was made, the total radioactivity of the injected dose at the time of assay being about 60 μC. Immediately after injection each rat was placed in a separate 500-ml. beaker fitted with a raised wire mesh. All beakers had previously been cleaned with chromic acid and distilled water.

Three hours after the injection the rats were made to urinate by the method described above, all urine being collected in the beaker. Although every effort was made to get complete emptying of the bladder, this was not essential to the accuracy of the test. The beakers and wire meshes were carefully rinsed with 5 ml. of distilled water projected against the walls by means of a syringe and needle. The washing fluid was collected in a small bottle. The ratio between Na^{24} and K^{42} concentration was determined in each sample by a method essentially similar to that of Tait and Williams (1952) and Simpson and Tait (1952) which involves measurement of the intensity of radiation with and without a thin aluminium screen.

Some modifications of the detail of the method were made. Only 0.2 ml. of the diluted urine sample was used for the radioactivity measurement, since this gave a sufficient number of counts a minute, from 5,000 to 10,000. This 0.2-ml. sample was placed on a disk of thin filter paper fitted into a nickel planchette 25 mm. in diameter. With the uniform distribution of this fluid thus obtained the radioactivity count could be made without drying the sample. Direct comparison showed that there was no significant difference between this wet method of counting and the method with dried samples used by Simpson and Tait. Counts were made on each sample, both with and without a filter screen composed of six sheets of 5/1000 in. (0.13 mm.) aluminium, and using a Geiger–Müller tube, G.E.C. type Z B 7, vw. 1400.

From the ratio of unfiltered to filtered counts the relative proportions of Na^{24} and of K^{42} in the sample could be derived by reference to a calibration curve constructed from mixtures of the two isotopes in known proportions. The degree of activity of the sodium-retaining factor in the extract under test was indicated by the fall in the ratio of Na^{24} to K^{42} in the urine sample excreted after the injection,

this ratio being expressed as a percentage of the mean figure obtained for the control group on the same day.

The principle of measuring the Na/K ratio rather than the actual excretion rate of either sodium or potassium alone was introduced by Simpson and Tait, and has several important advantages. It eliminates the need to collect and measure accurately the whole urine sample excreted by each rat. To achieve this reliably Singer and Venning had to ligate the urethras of all their rats and sacrifice them to obtain the bladder urine. When only the ratio is required completeness of collection is much less important. The rats were not sacrificed in our assays, but were used again two days later for similar assays, using another method with Na^{22} and K^{39} with subsequent estimation of the Na/K ratio by means of the flame photometer. In this paper only the results obtained by the isotope method are considered. A comparative study of the results obtained by the isotope and two other methods will be published elsewhere.

Preparation of Urinary Extracts

Owing to our uncertainty about the stability of the sodium-retaining principle, the extraction procedure was deliberately made as simple as possible to minimize the risk of destruction. Twenty-four-hour samples of urine were collected without preservative. These were extracted by manual shaking with 15 volumes per 100 ml. of urine, repeated four times with fresh lots of chloroform. No acidification of the urine was done before extraction, the *p*H usually being between 6 and 7. The chloroform extract was evaporated to dryness under reduced pressure, using a water bath at 50° C. Suitable aliquots were obtained by dissolving the residue in a small known volume of fresh chloroform, dividing this into small tubes, and blowing off the chloroform with a stream of nitrogen. For injection into rats the residue was dissolved in 20% ethanol in water, the volume being so chosen that the dose to be injected into each rat was contained in 0.1 ml. solution.

All extracts were stored dry until the day of assay.

Results

Under the conditions of our experiments a linear relationship was found between the Na^{24}/K^{42} ratio, expressed as a percentage of the mean figure for the control group, and the logarithm of the dose of deoxycortone injected. This relationship was found over the range of dose from 5 to 20 μg. per rat, and is shown in Fig. 1. Below 5 μg. per rat a linear relationship was not found, the ratio rising above the control level. In this respect our observations confirm the finding of Forsyth (1953) that very small doses of deoxycortone may actually have a sodium-excreting effect. Because of this excreting effect activities equivalent to amounts of deoxycortone less than 5 μg. could not be detected. It was considered desirable, therefore, to test all extracts at two dosages in order to increase the likelihood of obtaining an optimum content of the sodium-retaining substance. In this regard it is of interest that previous workers have usually failed to establish any quantitative relationship between size of dose and degree of response. Thus Luetscher *et al.* (1952) had found that increases in dose much above the equivalent of 20 minutes' urine output by the patient did not regularly yield a proportionate increase in response. Singer and Venning have also found sodium-retaining activity in the urine from some patients with nephrosis but had failed to get a bigger reponse with a larger dose of extract.

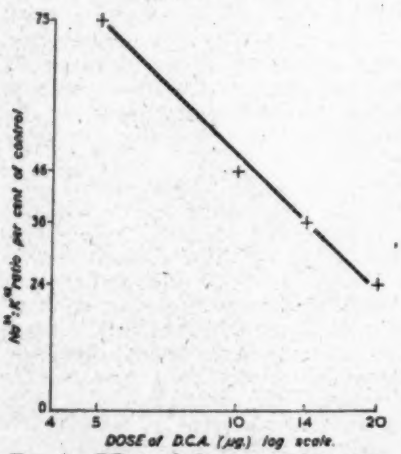

FIG. 1.—Effect of deoxycortone acetate. Linear relation between log. dose and percentage drop in Na^{24}/K^{42} ratio.

Five normal subjects have therefore been studied by injection of half-hour equivalent and of three-hour equivalent of urine extract into separate groups of six test rats. A sixth normal subject was also studied at the half-hour dose only. In four of the six subjects tested at the half-hour dose the ratio was depressed to 80% or less of the control level. An elevation of the ratio occurred in the other two (Fig. 2). This rise could have been due to a sodium-excreting effect of a very small dose of the active principle present in the extracts and comparable to the sodium-excreting effect of small doses of deoxycortone observed both by Forsyth and by ourselves. Support for this interpretation is found in the fact that both these extracts produced effective and significant depression of the ratio when given in the three-hour dose. With the other three extracts tested at both dose levels no significantly greater activity was observed at the higher dose than at the lower. Our experience of these extracts is thus the same as that of Luetscher *et al.* (1952) and of Singer and Venning (1953).

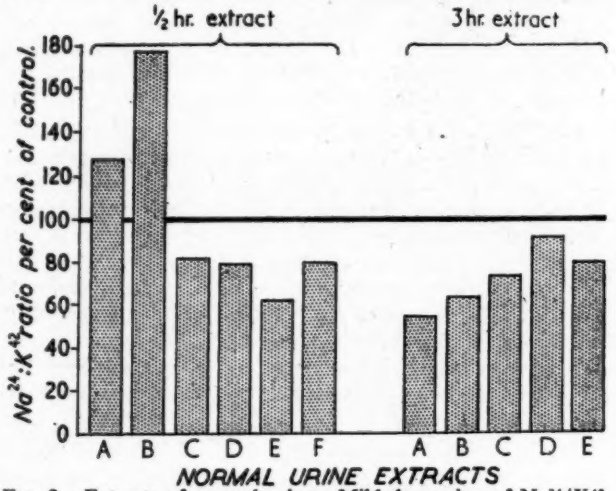

FIG. 2.—Extracts of normal urine. Mild depression of Na^{24}/K^{42} ratio.

Since the Na^{24}/K^{42} ratio can readily be depressed to a much lower figure by a sufficient dose of deoxycortone it would seem that the active principle whose effect is being observed in normal urine has very different pharmacological properties from deoxycortone itself. The results thus indicate the frequent presence of a sodium-retaining factor in chloroform extracts of normal urine, but they do not provide enough evidence on which to base an estimate of the amount present in terms of deoxycortone activity. Thus by reference to the deoxycortone calibration curve in Fig. 1, extracts C and E have respectively 4.5 and 6.5 μg. equivalents per half-hour sample. These figures correspond to 24-hour outputs of 216 and 312 μg. of activity expressed in terms of deoxycortone. On the basis of the three-hour assay, however, the same extracts showed activity indicating a daily output of active substance equivalent to only 40 and 35 μg. of deoxycortone respectively. Under such circumstances the assays are of little more than qualitative value.

They do serve, however, to show that such urinary extracts contain a principle which qualitatively alters the electrolyte excretion by the kidney. Methods of assay hitherto used have measured the effect on the rate of excretion of sodium only. Any factor in the extracts which may be toxic to the kidney and may cause a temporary impairment of renal function is likely to give a reduction in sodium excretion and thus, by a non-specific reaction, to suggest the presence of a specific sodium-

retaining factor. Any temporary impairment of renal function which may result from injection of the extracts is much less likely to affect the ratio of sodium to potassium. Changes in this ratio may be regarded, therefore, as a more reliable indication of the presence of a specific factor than will reduction in the rate of sodium excretion alone.

These results on normal urines may be contrasted with comparable assays on four patients suffering from rheumatoid arthritis. Extracts of the urine from these patients gave no indication of the presence of a sodium-retaining factor at either the half-hour or the three-hour dose. In Fig. 3 each column represents the mean effect on batches of five rats for each extract as compared with control groups of the same size.

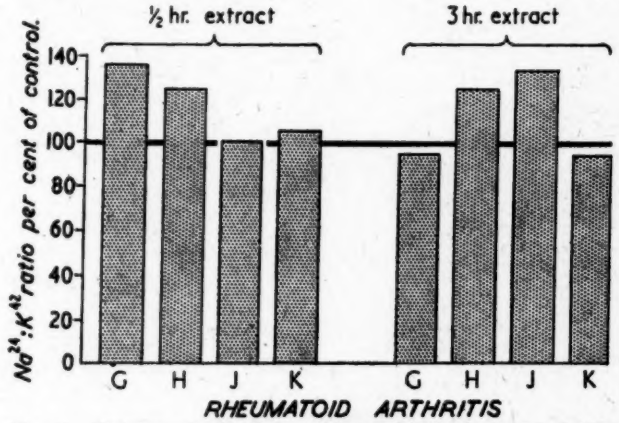

FIG. 3.—Extracts of urine from patients with rheumatoid arthritis. Failure to influence Na^{24}/K^{42} ratio.

In three patients suffering from congestive cardiac failure with gross oedema, results were less consistent. Subject P, with recurring ascites associated with severe tricuspid incompetence, showed no activity at two- or three-hour dosage. Subject F, losing oedema under mersalyl therapy, showed no activity at either half-hour or three-hour dose. On the other hand, subject M, with chronic congestive failure not improving under treatment, showed considerable sodium-retaining activity at the three-hour dose on two occasions.

These results on cardiac subjects merely confirm the findings of earlier workers that a sodium-retaining factor is present in human urine at certain times, but they do not assist in the prediction of the conditions under which it is likely to appear. Under such circumstances it is difficult to define more closely the properties of this elusive principle and to determine whether these properties coincide with those of electrocortin.

We have made several attempts to increase the output of this principle in urine to more manageable levels. The maintenance of a normal subject for a week on a diet containing less than 0.5 g. of sodium daily did not result in any detectable amount of the sodium-retaining factor in a subsequent urine extract. Similarly, the urine of a patient maintained on large doses of A.C.T.H., which was shown to have provoked a large increase in hydrocortisone output, did not show any significant activity. Thus neither of these procedures seems to lead to an increased output of the sodium-retaining factor (Fig. 4).

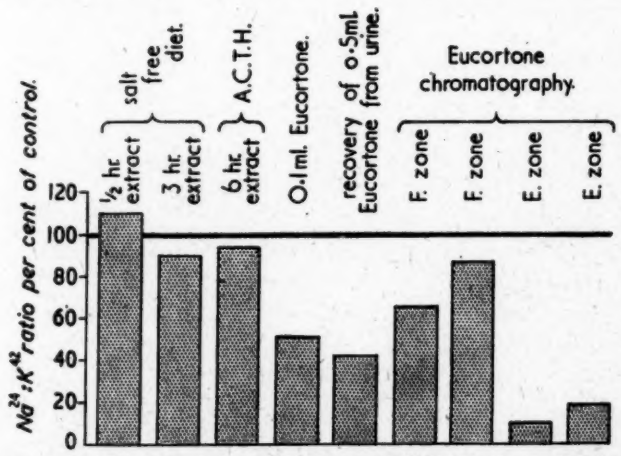

FIG. 4.—Effect of various extracts on Na^{24}/K^{42} ratio (see text). Electrocortin in "eucortone."

Detection of Electrocortin

Electrocortin can be distinguished clearly from deoxycortone by the rate of its flow on paper chromatograms. When the toluene/propylene-glycol solvent system is used electrocortin flows at almost the same rate as cortisone. While several other steroids have similar rates of flow in the chromatogram, it is very improbable that any other will combine a similar rate of flow on paper with a high degree of sodium-retaining activity. The demonstration of both these properties in an extract will thus establish the presence of electrocortin with a high degree of probability.

The most easily available source of electrocortin at present is commercial adrenal cortical extract. Using the Burroughs Wellcome preparation "eucortone," we were readily able to show that it contained strong sodium-retaining activity. When eucortone was added to urine samples and chloroform extracts were then made in the usual manner, these extracts also had strong sodium-retaining activity in our test. This activity ran in the cortisone zone. Though quantitative conclusions could not be reached it was clear that when electrocortin was added to urine a large proportion was recovered by the extraction procedure we were using (Fig. 4).

The chance discovery of a patient who proved to be excreting continually large amounts of the sodium-retaining substance in her urine has luckily enabled us to establish the approximate rate of flow of the principle on paper chromatograms and to show that this is the same as electrocortin.

The subject, Mrs. A, was a West African negress, aged 41, who was under investigation by Dr. M. D. Milne because of recurrent attacks of severe muscle weakness, which were found to be due to low serum potassium. Balance experiments conducted by Dr. Milne showed that she suffered from a very severe potassium-losing condition, apparently due to a renal tubular anomaly which was associated with a chronic pyelonephritis. Blood urea and pyelogram were normal; albuminuria varied between 1 and 3 g. per litre. At no time was there any oedema or other clinical evidence of sodium retention. Careful balance experiments showed that she was neither retaining nor losing sodium at the time of study. The full clinical history of this case with extensive electrolyte investigations is being published (Milne, 1954).

Three separate urine collections from this patient were tested and all showed strong sodium-retaining activity—much greater than we had encountered in any other subject. Depressions of the Na^{24}/K^{42} ratio with both half-hour and three-hour doses of extract are shown in Fig. 5. One of these highly active extracts, analysed for cortisone and hydrocortisone content by the chromatographic method described by Cope and Hurlock (1953), was found to contain 57 μg. of cortisone and 11 μg. of hydrocortisone a day. Thus a three-hour aliquot of this extract contained about 8 μg. of the combined hormones, a quantity much too small to influence the Na^{24}/K^{42} ratio in the tests. As may be seen from Fig. 5, an injection of 30 μg. of cortisone acetate per rat produced no detectable alteration in the ratio.

A sample of this extract equivalent to 48 hours' urine output was submitted to paper partition chromatography, using the toluene/propylene-glycol system. After a run of 72 hours most components of the extract had run off the bottom of the chromatogram, there being retained on the paper only those as polar as, or more polar than,

cortisone. Two zones were cut out from the chromatogram, one corresponding to the cortisone level (E) and the other to that of hydrocortisone (F). Both were separately eluted from the paper with methyl alcohol. The eluted fractions after evaporation of the methyl alcohol were then tested in the usual manner. The cortisone fraction showed a strong sodium-retaining activity, whereas no activity

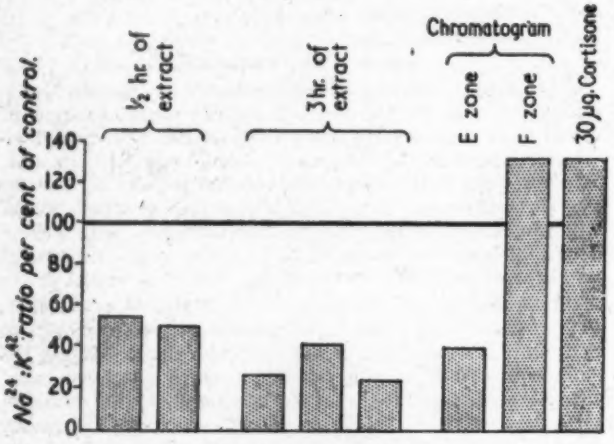

FIG. 5.—Strong electrocortin-like effect of urine extracts from Mrs. A. Activity confined to cortisone zone in the paper chromatogram.

was found in the hydrocortisone zone (Fig. 5). Thus the activity could be regarded as being due to electrocortin with a high degree of probability, the likelihood of any other substance combining a similar biological action with the same rate of flow on the chromatogram being extremely small.

Conclusions

The results obtained on normal urine extracts suggest the presence of small quantities of a substance having electrocortin-like properties, but they do not provide enough evidence on which to base any reliable estimate of the quantity present.

In contrast four urines from patients with rheumatoid arthritis all failed to show the presence of such a substance. It would be unwise to draw any conclusions from these relatively few cases, but, in view of the suggestions of Selye (1950) that disturbance of mineral corticoid production may play a part in the aetiology of rheumatoid arthritis, it is clearly of importance to determine whether such an absence of electrocortin from the urine is a regular feature of rheumatoid arthritis.

From the finding of activity in one of three patients with congestive cardiac failure examined no conclusions can be drawn. Although a high and maintained output of electrocortin by Mrs. A was demonstrated, it cannot be claimed that this throws any light on the nature of the peculiar renal and metabolic defect she was found to have. It is of great interest that in this patient there was ample proof that no sodium retention was taking place, and it must be concluded, therefore, that a high titre of electrocortin may occur in the urine in the absence of any sodium retention. Previous workers have claimed to find evidence of a sodium-retaining substance most readily in patients who were actively retaining sodium at the time. The fact that this patient was losing large amounts of potassium may, however, be of significance. It is at present quite unknown what are the relations between the level of steroid in the blood and the rate of excretion in the urine. Indirect evidence from the behaviour of hydrocortisone and allied steroids suggests that a rise in blood concentration is followed by a prompt increase in excretion. It is natural to assume, therefore, that a high output of electrocortin in the urine indicates a high concentration of this hormone in the blood, since it also is probably a very similar steroid. It is possible, however, that electrocortin may be bound to protein or even to potassium salts, so that its excretion rate is determined more by permeability changes in the kidney or by potassium output than it is by the concentration in the blood. In the present state of our knowledge of this hormone, however, any such suggestion must be purely speculative.

While this work was being prepared for publication a report appeared stating that Luetscher and Johnson (1954) have also been able to show that the sodium-retaining substance they find in the urine of nephrotic subjects runs on the paper chromatogram at a rate similar to that of cortisone. This substance also is therefore presumably electrocortin. Much work remains to be done before the significance of a high excretion of this new hormone by the human subject can be properly judged.

Summary

A substance having the power to increase sodium retention by the kidney has been found in large amount in the urine of a woman suffering from a severe potassium-losing condition. Other properties of this substance suggest that it is the adrenal hormone electrocortin.

Indications of the presence of a similar active substance in small amount in normal human urine have been found. No such active principle could be detected in four patients suffering from rheumatoid arthritis.

Our thanks are due to Dr. J. E. F. Bradley and D. G. Arnott for advice on the handling of isotopes, and to Miss Mary Standring for much technical aid.

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A medical school will form part of the Rhodesia University College at Salisbury, Southern Rhodesia, plans for which are now rapidly maturing. Last autumn the college's inaugural board visited London and discussed the college's foundation and constitution with H.M. Government, the Inter-University Council, and London University. As a result a capital grant of £1,250,000 towards the cost of its building and equipment has been promised from Colonial Development and Welfare funds, subject to the balance of the total capital cost (estimated at £2,000,000) and the annual maintenance costs (over £250,000) being found locally. The city of Salisbury has provided 458 acres as a site for the college. Land will be available near the new Salisbury Native Hospital for a medical school, and about 1,000 acres for an experimental farm. The first faculties to be established will be those of arts and science, and after that faculties of agriculture and medicine. The college will provide education for London University degrees and will be open to students of all races without discrimination. It is hoped that the college will be ready for teaching to begin early in 1956.

A DANGER OF PEPTIC ULCERATION

A SURVEY OF EIGHT CASES COMPLICATING SURGERY AND TRAUMA

BY

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In the last seven years eight patients have been observed whose convalescence from surgery and trauma had been interrupted by the appearance or the recrudescence of peptic ulceration. Of these eight patients five died, four as a direct result of their ulcers. It is therefore a complication to be feared, whether the preceding trauma be strictly causal or not. A connexion between trauma and ulceration has long been known, and has been recorded in the literature.

Curling (1842), inspired by the observations of Cooper (1839) and Long (1840), collected 11 cases of ulceration following burns, four of which he had treated in person in the wards of St. George's Hospital. Billroth (1867) first reported ulceration following operation, citing a case of death from gastro-intestinal haemorrhage on the sixth day after an operation to decompress a large retrosternal goitre. Von Eiselsberg (1899) described eight cases of ulceration, five fatal, mainly after operations for strangulated hernia. Busse (1905) and von Winiwarter (1911), from the same clinic, developed the theme; the latter collected 30 cases of gastro-intestinal haemorrhage after operations other than on the bowel, 17 of which were fatal.

Cushing (1932) described ulceration and necrotic mucosal lesions following intracranial operations and disease. He believed these to be due directly to lesions in the hypothalamus, and he instigated animal experiments, such as those of Hoff and Sheehan (1935), to corroborate this belief.

Penner and Bernheim (1939), in their study of the pathological changes in "shock," disputed Cushing's conclusions, and ascribed the ulcerating lesions to the non-specific stimulus of the shock. Herbut (1945) and McDonnell and McCloskey (1953) investigated the frequency of acute peptic ulcers in necropsies on patients dying within two months of operation, and found an incidence greater than could be explained by chance.

There have been sporadic reports of cases following trauma, such as those by Griffiths (1922), Ramond and Chêne (1932), and Gray (1945). There can be little doubt, therefore, that there is a relationship between peptic ulceration and the trauma both of accident and of operation. The cases here reported show that peptic ulceration may follow or be reactivated by injury and operation; that it may present as bleeding, penetration, or perforation; and that it may cause death, or be an incidental finding after death. A knowledge of this complication will result in its more frequent recognition and in the undertaking of the early and energetic treatment which it demands.

Case 1

A wizened man of 68 was admitted to Guy's Hospital on November 30, 1946, with a four-years history of indigestion and epigastric pain. Operation had been advised in June, as radiography had revealed a large gastric ulcer, which was probably malignant, but he had refused it. Later his symptoms had compelled him to change his decision.

On December 19 Mr. Grant Massie performed a high subtotal gastrectomy for a large carcinomatous gastric ulcer involving the pancreas. Progress was satisfactory until the evening of the fourth day, when there was a sudden onset of upper abdominal pain and rigidity, and the patient became shocked. In view of his poor general condition and the bad prognosis of the disease, it was decided to treat him conservatively. He sank steadily, became jaundiced, and died on the fifth post-operative day.

Necropsy showed an intact suture line and revealed no cause of the jaundice. At the oesophago-gastric junction and extending 3 cm. up the oesophagus there was an ulcer, triangular in shape, with its base 2 cm. in length. The floor was covered with purulent exudate and there was a perforation in the lower part into the peritoneal cavity, which was generally inflamed.

Case 2

A man aged 73 was admitted to the Radcliffe Infirmary under Mr. D. C. Corry on May 26, 1948, complaining of retention of urine for three days. He had been relieved by catheter daily, and his nearest hospital had been unable to admit him after he had travelled some twenty miles to its casualty department. His blood pressure was 220/110, and he complained of some giddiness on stooping. Apart from occasional "flatulence," he was well.

On the day of admission cystoscopy under general anaesthesia confirmed the presence of a large prostate and a trabeculated bladder. Vaso-ligation and retropubic prostatectomy were performed. Progress was good, and urine was draining freely through a urethral catheter until May 31, when he complained of nausea and melaena occurred. Blood was taken for cross-matching, morphine was given, and he was placed in recumbency, being allowed sips of water by mouth. His blood pressure remained at the post-operative level of around 160 mm. Hg systolic, his pulse was steady at 80 a minute, and he was comfortable. The next evening, however, the sixth after the operation, he suddenly complained of nausea again, vomited a large quantity of coffee-ground material, and collapsed. A transfusion of plasma was started immediately, and while the first pint of blood was being run into an arm vein he died.

Necropsy showed a healthy site of operation, and hypertrophy of the left ventricle. In the duodenum, 2.5 cm. from the pylorus, there was an ulcer just over 1 cm. in diameter with a little puckering of the surrounding mucosa and some fibrous thickening. Microscopy showed fibrotic and necrotic pancreas in the base of the ulcer, and polymorph infiltration of the mucosa. At one end of the ulcer there was a small arteriosclerotic vessel, the lumen of which was patent and completely eroded. The jejunum and large bowel were filled with some altered and some dark red semi-clotted blood.

Case 3

A man aged 51 was admitted to the Putney Hospital on November 11, 1949, having been concussed in a crash while on duty in a police car. He had been unconscious for about five minutes, but was then suffering from lacerations of his forehead, chin, and hands, which required a few sutures only. He had a tender right second costo-chondral junction with some bruising, but there was no radiological evidence of bone injury or any clinical evidence of trauma to the abdominal viscera. He was kept in bed under observation and was about to be discharged, when, on November 19, he complained of faintness and dizziness and passed a large tarry motion; at the same time he vomited a small amount of "coffee-grounds." There were no physical signs other than those of haemorrhage, and inquiry elicited no previous history of indigestion. He was treated by rest, sedatives, and two-hourly milk feeds; his haemoglobin dropped to 66%, but there was no further bleeding. On December 7 radiography showed that the duodenal cap was a narrow channel which did not relax, and in it there was a barium-filled crater. There was no local tenderness.

After this he was under observation as an out-patient with very few gastric symptoms. Radiography on March 3, 1950, showed a healed ulcer; and on June 2 there was scarring and spasm, but no tenderness. He was finally discharged on November 24, a year after the original injury, with no symptoms other than occasional indigestion relieved by medicine and diet.

Case 4

A man aged 76 was admitted to the Putney Hospital on December 31, 1949, having been knocked down by a car while wandering across a road; he had not been rendered unconscious, but had sustained various lacerations and bruises about the right eye, the right side of the chest, and the crest of the left ilium, which was fractured. His main injuries were bilateral compound and comminuted fractures of the tibia and fibula. There was very little clinical evidence of shock and after resuscitation he withstood very well toilet of his wounds, suture of the skin, and the application of plaster-of-Paris to both legs, which were then suspended from a Balkan beam.

In spite of his severe injuries he gave no cause for concern until January 13, 1950, at 9.15 p.m., when he complained of a sudden onset of severe abdominal pain and breathlessness. On examination he was sweating, was very restless, and was increasingly pale; his blood pressure was 120/80 and his pulse rate 100 a minute. There was no cyanosis or any abdominal physical signs, but rectal examination revealed tarry stools. There was a smell of blood, and while being examined he vomited a large amount of dark altered blood. Morphine was given intravenously and a blood transfusion was started as soon as possible, but he died at 10.15 p.m.

Post-mortem examination revealed recent bleeding from a chronic duodenal ulcer and further blood throughout the intestines. There was no evidence of abdominal injury, and no other gross lesion was found.

Case 5

A man aged 57 was admitted to Guy's Hospital on November 19, 1952, with an acute on chronic intestinal obstruction due to faecal impaction and a volvulus of the splenic flexure of a long redundant colon. He gave a history of a duodenal ulcer which had perforated seven years before, but which had given him no trouble for six years; his left kidney had been removed for stone eighteen years before this admission. The strangulated loop of colon was resected by the Paul–Mikulicz method on the same day, and on December 12 an attempt was made to close his double-barrelled colostomy extraperitoneally. After two small bowel actions the wound broke down and all his faeces discharged through the wound and continued to do so.

As there was an area of dermatitis round the fistula and as the abdominal wall was weak and scarred it was felt that further operation should be postponed. He was therefore discharged on February 1, 1953, rather against his will. It was hoped that repeated rectal wash-outs might remove the faeces that kept impacting in the distal bowel, and that his fistula might close spontaneously.

His domestic arrangements were ill suited to this regime, and the dermatitis round the fistula became worse. Shortly after discharge he complained of fullness after meals and epigastric pain going through to the back. On March 9 he was readmitted as an emergency because for the last two days he had passed profuse, tarry, ill-smelling motions, and had become faint and giddy. He was pale, his pulse rate was 106, and his blood pressure 120/75. Rest, morphine, and two-hourly milk feeds were prescribed, and during the next few days five pints (2.7 litres) of blood was transfused. Frank melaena was present on only two more occasions, but occult blood was repeatedly present in his stools; a fractional test meal showed blood in all specimens and a high total acidity. At laparotomy on April 7 Mr. Wass found a duodenal ulcer with signs of recent activity and some fibrosis extending into the pancreas. A partial gastrectomy was done with a retrocolic valvular gastro-jejunostomy. Finally on June 4, after repeated evacuations of faecal masses in the sigmoid colon, the fistula was successfully resected and the remaining colon anastomosed. On June 27 he went away for convalescence. He has since been seen, well and free from symptoms.

Case 6

A man aged 71 was admitted to Guy's Hospital on March 30, 1953, with symptoms due to an anal neoplasm of two months' duration. Biopsy the next day showed this to be an epithelioma of the anus infiltrating the sphincters. On April 14 a synchronous combined abdomino-perineal excision of the rectum and anus was done by Mr. Wass and myself; recovery was uneventful, apart from some sepsis in the abdominal wound. On April 27 he began to complain of epigastric pain and fullness; on April 29 he vomited 12 oz. (340 ml.) of dark material in which were seen "coffee-grounds." On questioning he admitted to having been treated two years before by his own doctor for ulcer symptoms. He had been put on a diet, to which his symptoms had responded, but no radiography had been performed. A diagnosis of duodenal ulcer was made, and he was treated with alkaline powder and atropine, his symptoms soon resolving. On May 14 a barium-meal examination showed that the stomach and duodenum were much displaced and distorted by an enlarged and tender head of the pancreas; further radiography on May 21 showed that this distortion was no longer present, but that there was a trefoil deformity of the duodenum with ulceration. On May 5 he was transferred for treatment of his anal neoplasm by radiotherapy; 2,500 r was administered to both groin fields, and no further digestive upset occurred.

Case 7

A spinster aged 68 was admitted to Guy's Hospital under Mr. Wass on May 31, 1953, complaining of "piles" for one year, malaise for six months, and constant watery diarrhoea for six weeks. She was a retired lady almoner who had lost 14 lb. (6.4 kg.) in weight in the last eight weeks. On examination she was pyrexial and looked ill; she had lower abdominal distension, especially marked in both iliac fossae. Rectal examination revealed at the fingertip a hard mass filling the upper pelvis. On June 9 at laparotomy the large bowel was found to be grossly distended and hypertrophied as far as the lower sigmoid, where there was a mass, the size of a foetal head, stuck to the left wall of the pelvis and to the bladder. A left iliac colostomy was fashioned to relieve the obstruction. For a week she did well, apart from an inability to pass urine unaided by catheter. Her colostomy worked well at first, but she then began to get colicky abdominal pain and her temperature rose. Attempts to break up hard faecal masses in her proximal colostomy loop were only partially successful, and she died on June 19, ten days after operation, in coma, with a temperature rising to 106° F. (41.1° C.).

At necropsy some smooth-walled cysts and two cavernous haemangiomata were found in her liver; the main cause of death was a peritonitis from two perforated stercoral ulcers of the colon proximal to the colostomy. The primary lesion was found to be a necrotic adenocarcinoma of the upper rectum, involving bladder and perirectal tissue, 10 cm. in diameter. In the first part of the duodenum there were five ulcers 0.5 to 1.5 cm. in diameter; from the floor of the largest projected a pedunculated blood clot which formed a cast of the duodenum. This ulcer had also penetrated the posterior wall of the duodenum, and a haematoma had formed between this and the pancreas. Microscopy showed an acute deeply penetrating ulcer.

Case 8

A man aged 74 was admitted to Guy's Hospital on September 15, 1953, under Mr. Law, complaining of increasing dimness of vision from his right eye for nine months. He had had a gastro-jejunostomy performed in

1912 for duodenal ulcer, since which time he had been troubled little by indigestion, save for a haematemesis in 1947, for which he had refused hospital treatment. On September 16 his right eye was removed for a malignant melanoma, with no local complications.

On September 22 he vomited altered blood on two occasions and passed a melaena. His general condition responded initially to blood transfusion and morphine, but he failed to maintain progress, dying on September 25.

Necropsy seven hours after death showed clean wounds and no local tumour cells, but microscopy of the liver revealed a minute melanotic deposit in one hepatic portal duct. His abdomen showed gross distension of the stomach and upper jejunum with thin grumous fluid. There was a retrograde ante-mortem intussusception of mid-jejunum, with the distal small intestine empty of contents and contracted to the size of a lead pencil. The large bowel was full of concentrated altered blood of various ages.

A retrocolic gastro-jejunostomy and four peptic ulcers were seen. Two were apparently of long standing—one on the lesser curve of the stomach and one on the jejunal side of the suture line. Two were recent—one in the fundus of the stomach and one in the jejunum about 2 cm. from the suture line.

Microscopy of the lesser-curve gastric ulcer showed a fibrous-tissue floor with two vessels filled with organizing thrombus; the mucosa showed some recent necrosis and infiltration with round cells and plasma cells, which suggested recent ulceration on the site of a long-standing ulcer. Microscopy of the distal jejunal ulcer showed the vertical edge characteristic of acute ulceration with the histological picture of acute mucosal destruction.

Discussion

Eight cases of proved peptic ulceration arising after trauma are presented. All the patients (seven male and one female) were over 50 years of age, the average being 67; four died as a direct result of the ulceration; in two cases the ulcers were multiple and in one they were an incidental finding at necropsy. The time interval from the original trauma to the first symptom varied from four days to ten weeks, but in seven of them it was from four to thirteen days. The original trauma varied widely.

The mechanism whereby this ulceration arises is a matter for conjecture. In Case 1 it may have been due to the pressure of the intragastric Ryle tube, but this was in place for only three days and the ulcer was much bigger than any such area of pressure. The direct trauma of the operation might be blamed, but the lower oesophagus and upper stomach share a blood supply, and the ulcer, which had the appearance of a typical peptic ulcer, stopped abruptly at the cardia. The vascular disease responsible for the hypertension in Case 2 might have been contributory, but the coronary arteries were only moderately atheromatous and the kidneys were normal. A direct injury to the abdomen might have originated the ulcer in Case 3, but there was no haematemesis at the time or any bruising of the epigastrium.

Physical disturbance in the form of severe shock was a feature in only one patient (Case 4), who had compound comminuted fracture of both lower limbs. None of the operations were minor, but none of the patients were unduly affected by them.

Mental disturbance may have been a factor in some. Case 1 evidently lay in dread of operation, having refused one previously; Case 2 had had the distressing experience of transport several miles to a hospital which had refused admission and sent him home again; Case 5 desperately wanted his faecal fistula closed, as his home conditions were quite unsuited to its care. On the other hand, no one could have seemed more placid than Case 3, who was quite unruffled by his illness.

An attractive hypothesis would be that the ulceration is the result of the excess secretion of adrenocorticotrophic hormone or cortisone during the adrenergic-corticoid phase of Moore (1953). The effects on the gastric secretion of these hormones have been well described by Gray *et al.* (1951).

A previous history of indigestion was given by two patients: Case 2 admitted to occasional flatulence and Case 6 had been treated with diet for ulcer symptoms for two years previously. In two there was a history of ulcer: Case 5 had suffered from a perforated duodenal ulcer seven years before his admission, and Case 7 had had a gastro-jejunostomy performed 41 years before for duodenal ulcer. But neither of the two with a history of ulcer had been troubled with symptoms for six years.

Summary of Cases

Case No.	Sex and Age	Operation	Presenting Symptom	Ulcer	Result	Interval to Symptoms	Interval to Death (days)	Comment
1	M 68	Subtotal gastrectomy for carcinoma of stomach	Perforation	Oesophageal (juxta-cardiac)	Died	4 days	5	Had refused operation for carcinoma 4 months previously
2	M 73	Prostatectomy for urinary retention	Melaena	Duodenal	"	5 "	6	Had been admitted after 3 days' catheterization and after being refused admission by another hospital. History of occasional "flatulence"
3	M 51	Road traffic accident, concussion and minor lacerations	"	"	Survived	8 "	—	No epigastric injury
4	M 76	Road traffic accident, compound fractures both tibiae and fibulae	Pain and melaena	"	Died	13 "	13 plus 1 hour	No epigastric injury. Sudden pain and collapse with death during transfusion
5	M 57	Volvulus of large bowel, attempted closure of faecal fistula	" "	"	Survived	10 weeks	—	Perforated D.U. 7 years before; no symptoms for 6 years. Sore skin round fistula and desperately eager for closure
6	M 71	Abdomino-perineal resection for epithelioma of anus	Pain, fullness, and coffee-ground vomit	"	"	13 days	—	Two years ago "ulcer" symptoms treated by own doctor by diet with success
7	F 68	Colostomy for massive infiltrating carcinoma of upper rectum	None	Duodenal (multiple)	Died	—	—	Incidental finding at death from perforation of stercoral ulcers in bowel proximal to colostomy
8	M 74	Enucleation of right eye for malignant melanoma	Melaena and haematemesis	Gastric and jejunal	"	6 days	9	Gastro-jejunostomy 41 years previously. Haematemesis 7 years previously

In those cases in which microscopy of the lesion was carried out the results have been reported. That it was not done in every case is no great defect: microscopical evidence of chronicity is probably unreliable (Tanner, 1953). Clinical differentiation of acute from chronic ulceration is also arbitrary. At one end of the scale is the patient with severe symptoms for many years, who at laparotomy is found to have a minimal lesion; at the other is the patient—often elderly—who has no symptoms until haemorrhage or stricture ensues, and who is found to have a gross chronic ulcer. However, from a consideration of these cases it would appear that the earlier a patient dies the more acute the appearances (Case 1); and the longer he survives the more chronic these are (Case 4).

More important from a clinical aspect would seem to be the anatomical site of the ulcer (see Fig.) and whether its

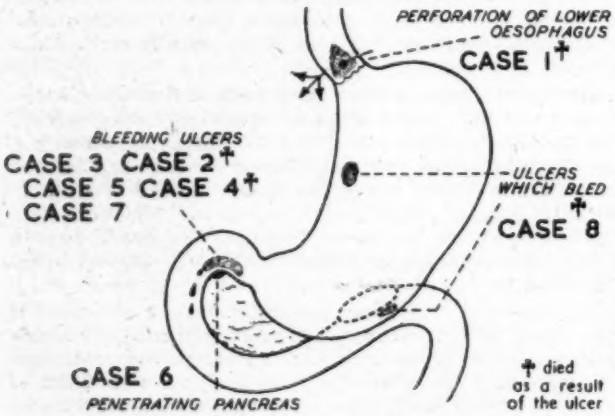

Diagram showing the anatomical site of the ulcers.

base is formed by peritoneum (Case 1), pancreas (Case 6), or blood vessel (Case 4). Perforation or haemorrhage brings a grave prognosis to elderly patients who are convalescing from accident or surgery, and in six of these patients the main symptom was haemorrhage.

It is apparent from a study of these cases that there may be some warning that ulceration is taking place. There was none in Cases 1, 4, and 7 (all of whom died); but there was warning with Cases 2, 3, 5, and 6 (of whom one died), and it is possible that early treatment might have saved life.

Conclusions

Peptic ulceration after trauma may be regarded as the abnormal reaction of an ulcer-prone patient to a physiological stimulus. Until such a time as the physiological reaction to stress and trauma can be measured and safely regulated, the best way to deal with this complication would be by prophylaxis and by early recognition and treatment. Prophylaxis is difficult, as the ulcer-prone patient does not declare himself. It is not the practice of surgeons to ask patients awaiting consultation to fill in "pro formas" on personal habits and previous and family history; were it so, however, it would be worth asking, "Have you suffered much from indigestion?" or, "Do you take stomach powders, tablets, or mixtures?" and if the patient be over the age of 50 and a man particular heed should be paid to such an admission. A careful general history is as important in surgery as it is in medicine.

If such a history is elicited the regime after operation should not be too active, and inquiry should be made into upper abdominal symptoms. In addition to the daily examination of the calves, a hand might well be applied to the epigastrium. If relevant symptoms appear, antacids and atropine should be given, and if tarry stools are passed the matter should be reported immediately, a serious view taken, and arrangements made at once to collect serum for cross-matching in preparation for a transfusion of blood that may be needed with great urgency.

Summary

Eight cases are presented of ulceration arising as a complication of operation or injury.

This ulceration may arise *de novo* or may be an exacerbation of previous ulceration.

A watchful outlook should be maintained for epigastric postprandial pain; particularly in the early convalescent phase. Melaena and coffee-ground vomit must be recognized as alarm signals, and immediate steps should be taken to arrange for rapid blood transfusion if necessary.

Energetic medical treatment may well avert death from a complication which has a high mortality rate.

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RECENT EXPERIENCE OF ENCEPHALITIS IN CHILDHOOD

BY

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This communication is based on a clinical study of 93 children with encephalitis seen since 1946 in the children's wards of three hospitals associated with the Department of Child Health in the University of Durham. This experience has been so varied that it invites an attempt to analyse it.

The term "encephalitis" is used without attempting to indicate any particular aetiological factor, whether of virus, allergic, or toxic origin. What is meant, therefore, is the occurrence, in a previously healthy child, of the classical symptoms or signs of disturbed cerebral function, which, after the exclusion of bacterial and vascular conditions and of chemical poisonings, are presumed to be the result of non-suppurative disorder of the brain.

The patients fall into two groups: (1) those associated or following on a recognized infective condition (measles, 12; pertussis, 8; varicella, 3; rubella, 1; mumps, 1; herpes simplex, 1; acute rheumatic fever, 1; infectious mononucleosis, 1), of which there are 28; and (2) those of unknown aetiology with no obvious causative factor, of which there are 65.

In attempting to define the clinical pictures of these diseases, this material could have been dealt with in two

ways. First, the cases associated with known infections might have been analysed to see if each had a distinctive clinical picture, and those of unknown aetiology could then be related to or compared with them. Bearing in mind that encephalitis may be the only manifestation of infections such as mumps, measles, and rubella, studies such as those of Greenfield (1950) have been of immense value in indicating the variety of conditions which can give rise to encephalitis, but they have been concerned solely with fatal cases and, even so, have shown quite clearly that there has been no uniformity of the clinical pattern in the various pathological groups. Second, all the cases might have been analysed according to the pattern of the clinical illness, regardless of aetiology or pathology, to ascertain whether any types were discernible. It is realized that in the absence of virus and histological studies, cases of encephalitis lethargica, subacute inclusion encephalitis (Dawson, 1933, 1934), haemorrhagic encephalitis (Baker, 1935), acute haemorrhagic leuco-encephalitis (Weston Hurst, 1941), and polioencephalitis (McAlpine *et al.*, 1947; Brewis and Neubauer, 1948; Jennings *et al.*, 1949; Kelleher *et al.*, 1949; Barrett *et al.*, 1952) may be grouped together in this way. This second method of analysis was chosen because it reveals clinical patterns of illness, irrespective of aetiology, which offer guidance to the practitioner in giving a prognosis.

Four main patterns of illness have been distinguished, although in this attempt at classification it has not been possible to insist on rigid criteria, and many of the signs and symptoms of impaired function of the nervous system have been common to all. Only the more obvious differences in onset, course, and duration have been used, and in some minor respects overlap between the types has occurred; in addition to which many cases could not be classified and have been described as a heterogeneous group.

Type 1.—Cases presenting as a sudden cerebral calamity in a previously healthy child or following an indefinite prodromal phase. Convulsions were prolonged or repeated, and unconsciousness lasted several hours or even two to three days. The duration of the acute phase was short, death or returning consciousness occurring in two to three days.

Type 2.—Cases beginning usually with a non-specific and meningitic illness with pleocytosis in the C.S.F. and followed by the acute onset of unconsciousness, stupor, or somnolence of a few days' duration, from which a rapid or sudden recovery frequently occurred. Cranial nerve paralysis and lower motor weakness were often encountered and recovery was the rule.

Type 3.—Cases often with a prolonged and insidious prodromal phase of indefinite symptoms or occasional convulsions, with periods of well-being followed by gradual unsteadiness developing into gross ataxia, tremors, and continuous choreiform movements of the whole body, particularly of the eyes. The illness was long, and was associated with emotional instability. Usually these cases had been diagnosed as chorea or cerebral tumour.

Type 4.—Cases which resembled encephalitis lethargica, with a short prodromal phase, and a slowly developing somnolence or coma. This lasted several days and was followed by cranial nerve involvement and a slow return to consciousness, interrupted by mental and emotional instability.

Type 1. Sudden Onset with Convulsions and Unconsciousness

Illustrative Case.—A. G., aged 10. On previous day, shivering, restlessness, and vomiting; no headache. Later unable to speak; convulsion with bilateral clonic movements lasting 1½ hours. Temperature 107.8° F. (42.1° C.) reduced to 101° F. (38.3° C.) by sponging. On admission gravely ill, unconscious and vomiting; limbs immobile and flaccid. Face constantly twitching; eyes deviated, coarse nystagmus. No meningeal signs; C.S.F., 22 lymphocytes. Reflexes absent; W.B.C., 32,300. Remained unresponsive, with sporadic twitching of right hand, fingers, and toes; later, tonic neck reflexes present; head and eyes deviated to right, with facial weakness and hemispasticity. Constant variation in physical signs. Rapid deterioration, death 33 hours after first convulsion. Necropsy revealed small perivascular haemorrhages and cuffing in right basal ganglia, frontal cortex, brain stem, and spinal cord, and also perivascular collections of round cells in areas of the occipital and parietal cortex. No neuronal changes.

There were 19 cases of unknown aetiology in this category, 13 of them being below the age of 2 years. In nine there had been prodromal symptoms of malaise, listlessness, slight cold, and restlessness for one to five days. Eleven patients had vomited, six had loose offensive motions, and two had abdominal pain, although the bowel disturbance did not usually continue into the illness. In addition there were three cases of measles, four of pertussis, one of mononucleosis, and one of mumps which were similar in type.

Convulsions, generalized in 21 cases and limited to twitching or spasms of the face or limbs in 7, varied in number from 2 to 50 before admission. They had been continuous in 17 patients, and after admission were still continuous in 13, of whom 7 died. All patients were unconscious or stuporous from the onset of the fits. The temperature was raised in all but five, a high rising temperature being associated with a bad prognosis. Meningeal signs were present in only four cases due to measles or where the aetiology was uncertain, but were present in five of the other six cases of known infection. The C.S.F., examined in 26 cases, was normal in 18, while there was a mild pleocytosis of 12 to 56 cells in the remaining eight, one of which was blood-stained. Of these latter cases five were fatal.

The subsequent course of the illness in the survivors was very variable. Convulsions recurred in six cases and lasted for a few hours; drowsiness or coma for a day or two, accompanied by retardation, aphasia, slurring of speech, spasticity, choreo-athetosis, and ataxia were seen. Often recovery was quick, the illness lasting a week or less in nine cases, one to two weeks in four, two to four weeks in five, and two months in one case. The longer the illness the more likely were sequelae to develop; two cases were left hemiplegic with fits, three mentally retarded, and one with fits. Hemiplegia occurred in three other cases, one a fatal case and the others recovered completely.

Nine patients died, usually after short illnesses—six of 48 hours, two of three days, and one of 16 days. The last-mentioned case was that of a baby who continued to have convulsions for 10 days after admission and died a few hours after ventriculography. At necropsy, infiltration and old haemorrhages into the arachnoid were the only findings. Perivascular demyelination and haemorrhage were found in the mid-brain of one patient and the cortical areas of another; while perivascular cuffing and neuronophagia of polioclastic type, petechial haematomata, and capillary thrombi with infiltration were the appearances respectively in the other three patients on whom necropsies were done.

Type 2. Acute Onset with Short Somnolent Phase and Paralyses

Illustrative Case.—D. D., aged 10. Headache, sore throat, and fever lasting one day; then well for five days. Relapsed with pain in neck, headache, and sleepiness. Vomited continuously next day, but rational and co-operative. Marked meningeal signs, nystagmus, and right facial weakness, diminished tendon reflexes. Temperature 101° F. (38.3° C.); C.S.F., 45 cells, mainly polymorphs. Subsequent deterioration with deepening coma lasting five days, bilateral facial palsy, weakness of left arm and right shoulder, and diffi-

culty in swallowing. Slow improvement; becoming rational, though incontinent, excitable, and difficult to control. Went home 18 days after admission with paralysis of right face, deltoid, and left thigh, and emotionally labile. Went through a difficult phase, being bad-tempered, excitable, and nervous; often rude and vulgar. Speech staccato; appetite voracious; thin and restless. Eighteen months later had steadied down was doing well at school, and had recovered neurologically.

There were 15 cases in this category, all of unknown aetiology, all children in their early years, and most were encountered during outbreaks of poliomyelitis. Thirteen had some form of prodromal illness lasting two to eight days and consisting of headache, vomiting, fever, transient diplopia, disturbance of micturition, drowsiness, aphasia, and dysphagia. Fits were present in three cases, and in two cases siblings had a febrile meningitic illness about the same time. All but three were febrile. Meningeal signs were present in 12 cases, but in all there was a pleocytosis in the C.S.F.

The mental state on admission was variably described as: unconscious (2), stuporous (3), persistently asleep (3), retarded but rousable with difficulty (4), uncontrollable following three days' somnolence (1), conscious but aphasic (1), rational, becoming semicomatose for a week later (1).

Recovery of mental clarity occurred early: nine patients became conscious on or before the fourth day, four during the next three days, and only one took longer than a week. Sometimes this return of consciousness was very dramatic and sudden; a child having been deeply asleep or semicomatose for some days would waken in a few hours and become quite alert, would be found wandering round the cubicle, or, in one case, drinking out of the cubicle tap. Similarly, the return of speech followed the same pattern, and so striking was this apparent transformation from lethargy and sleep that the condition became known as the "Snow White syndrome."

The cranial nerves were not infrequently involved; strabismus (1), ptosis (1), facial palsy (3), aphasia (4), dysphagia (3). Paralysis of an arm or a leg occurred once each, and only five cases failed to show some form of lower motor weakness at some stage of the illness. Pyramidal signs were seen in six patients.

Only one death occurred: that of a 14-year-old child who was stuporous but responding on admission, and who became progressively comatose and died on the fourth day. At necropsy the lumbar cord was congested and showed punctate haemorrhages anteriorly, and perivascular cuffing was seen in the cervical cord and the thalamic region.

In only three cases did permanent sequelae persist: two cases of unilateral facial palsy and one of foot-drop; although temporary emotioual instability was occasionally encountered.

Type 3. Insidious Onset with Continuous Choreiform Movements and Ataxia

Illustrative Case.—E. R., a male child aged 18 months. Previously well; then off his feet slowly; began to shake. and eyes moved from side to side. Very miserable; no temperature; C.S.F. normal. Seen again in one month; no progress and still very ataxic. A month after this, although bright and friendly, he had difficulty in balancing even when sitting still. His head was moving up and down regularly, and he was making mouthing movements. Unable to crawl, but could roll over. Reflexes, fundi, and C.S.F. normal. W.R. negative. E.E.G. indefinite. Developed basal ganglion tremor, particularly in arms. Excessive salivation. Improved for a time and could crawl. and the involuntary movements almost disappeared. Three weeks later he had again deteriorated, and the tremors were as bad as before, affecting head, eyelids, mouth, and to a less extent the limbs, and being continuous in sleep. These movements gradually became worse; arms, legs, and head jerked about uncontrollably; the eyes were never still, and rolled upwards. He became uncooperative and resented interference. His condition was unchanged a year later.

There were nine cases similar in type to this, all of unknown aetiology, and all except one were under 5 years. There was an insidious onset from two weeks to three months, and occasionally isolated fits occurred two to three weeks beforehand, followed by a period of well-being before the characteristic signs developed. Sometimes a gradual unsteadiness of the limbs was the first manifestation, followed by stumbling and ataxia with tremors, squints and continuous eye movements or oculogyric crises, or a typical chorea-like illness. In four cases irritability, hysterical behaviour, or personality changes were also present, and frequently these patients were thought to be suffering from an intracranial tumour. The temperature was normal in all except one case.

The patients might be co-operative, lying quietly and slightly drowsy, or irritable, wildly excited and restless, violently choreiform and ataxic, with gross nystagmoid movements of the eyes. Coarse tremor on voluntary movement, nodding of the head, jerky speech, and salivation were present in some cases. Meningeal signs were seen in only one case, the C.S.F. contained a few cells in four cases, and the Lange curve carried out in five was normal. The subsequent course was usually slow improvement, often punctuated by relapses, emotional lability, staccato speech, outbursts of temper or excessive cheerfulness, and with slowly improving ataxia. The illness was usually long—between two and three months from the onset—although in two cases it was only two to three weeks.

Two patients died: one with continuous writhing and twitching, upward deviation of the eyes, slow deterioration, and finally opisthotonos with death in the eighth week; the brain showed occasional microscopic haemorrhages and signs of neuronal degeneration. The other case showed a progressive increase of the choreiform movements, alternating with phases of quiescence, when the temperature subsided for a time, but, following mental degeneration and blindness, the illness terminated in a convulsion in the seventeenth week. Minor changes with neuronal degeneration were seen in the mid-brain and cervical cord.

Sequelae were not infrequent: only three cases left hospital apparently normal; one was unchanged and had gross tremor and ataxia, myoclonus, and eye movements more than two years later; one was abnormally restless; one was irritable and domineering; and another was attending a psychiatric clinic.

The cases of this type were very similar in description to those of subacute inclusion encephalitis, although the normal Lange curves in four cases and the subsequent course did not conform to the usual fatal result or complete disablement reported by most observers (Campbell *et al.*, 1952; Foley and Williams, 1953), and at necropsy in two cases no inclusions were found.

Contrasted with the prolonged illness and very marked disturbance of cerebral function, the pathological changes were surprisingly scanty.

Type 4. Somnolent and Lethargic Illness with Spasticity and Retardation

Illustrative Case.—B. H., a boy aged 4¼. Illness began two days before admission, with abdominal pain, repeated vomiting, and large offensive stools; drowsy; temperature 101° F. (38.3° C.), but no abnormal signs. On morning of admission he was found in a state of coma, with slight muscular rigidity and bilateral extensor responses; mild meningeal signs; C.S.F. normal. If undisturbed he lay as though peacefully asleep, but he resented interference, grimacing and crying, but otherwise aphasic. The face had an "ironed-out" appearance, and, although occasionally his attention was attracted, lethargy and sleep rapidly returned. Breathing was shallow and periodic, with deep sighing; inability to swallow necessitated tube-feeding almost continuously for six weeks. State of consciousness varied;

flexibilitas cerea developed and increasing spasticity—in the arms, of "cogwheel" type. Illness complicated by hypostatic pneumonia, generalized rigidity, double incontinence, and thrombosis of the inferior vena cava, the last-named being compensated by large venous anastomoses over the abdominal wall. Slow improvement occurred, and emotional responses returned, together with ability to swallow and a decrease in spasticity. Further progress was relatively rapid, rigidity of the left side of the body being slower to recover than the right. Euphoria and emotional lability were seen for a long time and walking was ataxic. He left hospital in three months, and when seen one year later was happy but somewhat backward, and still had slight spasticity of the left arm.

Five cases of unknown aetiology showed this type of illness—an infant and four young children. Prodromal symptoms were present in all, lasting from two to three days to one week. They consisted of headache, vomiting, abdominal pain, screaming and staring, occasionally twitching or a definite fit. In addition in this group there were seven cases of measles, three of pertussis, one of acute rheumatic fever, and one of rubella.

Meningeal signs were present in nine cases and a pleocytosis up to 150 cells in eight—not always the same cases. When first seen these patients were comatose or apparently deeply asleep. The cranial nerves were often affected, squints (9), ptosis (3), facial paralysis (9), pharyngeal paralysis (7), and a mask-like face or "dead-pan" appearance (5) being seen.

The course of the disease varied in duration up to two and a half months, five cases due to the acute infections had illnesses lasting one to two weeks only. Usually the drowsiness or coma increased for a few days, then improved gradually, being followed by variable periods of stupor, aphasia, dysphagia (two cases required tube feeding for three to six weeks), wild tremor and ataxia, twitchings and occasional unilateral or bilateral fits, spasticity with extensor responses, flexibilitas cerea, irritability, screaming, salivation, and yawning. There was no sudden awakening from the lethargy such as occurred in the Type 2 cases.

There were two deaths, both in measles cases; 10 cases recovered completely; two were much improved but were mentally reduced; and one was apparently of normal intelligence but excessively noisy. One of the measles cases was backward, with infantile speech; another, who left hospital in a hopeless state and was little better a year later, when seen five years after the illness was second in his class at school, though his temper was uncertain. One pertussis patient was also left mentally retarded.

Cases with a Varied Clinical Picture not Resembling Other Types

There were 24 cases, 17 of unknown aetiology, which could not easily be placed in any of the other categories, although they showed certain similarities to them, often to more than one type. In many there were bizarre features; one child attacked another in the next bed and had alternating phases of aggression and docility; eventually he was transferred to a psychiatric ward, where he had several fits followed by stupor for three weeks. He made a complete recovery.

Three cases were thought to be associated with sensitivity reactions, sulphadimidine and "sulphatriad" probably being the responsible agents in two instances. The rashes were all urticarial and of mixed type, showing morbilliform, scarlatiniform, and petechial elements. There was sudden onset of drowsiness and slurred speech or aphasia. All had extensor responses, two were pyrexial, and initially the C.S.F. was normal in all, though later one showed a pleocytosis of 24 cells. Recovery was rapid, within two to three days, and with fading of the rash. One has a persistently abnormal E.E.G. and violent bursts of temper.

Four cases had illnesses resembling cerebellar tumour in which a variable period of dysphagia, dysarthria, disorientation, and fits preceded nystagmus, cerebellar ataxia, and sometimes indefinite pyramidal signs. So marked were these signs that air encephalography was carried out in one case, with negative results. A diagnosis of tumour was originally suggested in many cases in the whole series, but exploration was carried out in only three other cases.

There were three cases following varicella which had a not dissimilar appearance to those just mentioned, but the diagnosis was never in doubt, and they all recovered quickly.

In two cases there was an illness progressing over five and sixteen days respectively, consisting of headache, vomiting, drowsiness, and apathy, and in one a fit, followed by a slowly developing hemiplegia. The temperature was normal and meningeal signs were absent; the C.S.F. in one case contained 22 cells, the other fluid being normal. On admission the patients were apathetic or fretful, becoming increasingly drowsy for a few days. One recovered from the hemiplegia in three weeks; the other was left with a spastic hemiplegia and an impulsive temperament. These cases were not unlike those described by Weston Hurst (1941), except that neither was fatal.

The remainder of this group were made up of two cases of measles, one of pertussis, and one of herpes simplex which could not be classified elsewhere.

The fatal case was that of a child of 3 months who was taken ill suddenly with continuous loud screaming and extreme restlessness. The temperature was only 99.3° F. (37.4° C.), and vomiting was absent. Apart from a depressed fontanelle, there were initially no abnormal signs. The screaming continued for five days, and was followed by unconsciousness and generalized spasticity. The C.S.F. was repeatedly blood-stained, was under normal pressure, and later became xanthochromic. The child lay completely unresponsive, developing nystagmus and intermittent squints and bilateral optic atrophy, apparently being blind and deaf. The limbs remained spastic, with occasional tremulous movements. The fontanelle later became tense, but otherwise the condition remained unchanged for three months, when, following a short period of continual spasms affecting the limbs, and hyperthermia, the child died. Different diagnoses had been entertained at different times, among them Schilder's encephalopathy, cerebral venous thrombosis, and cerebral sclerosis of Krabbe; but at necropsy the changes, though not gross, were compatible with haemorrhagic leucoencephalitis.

Four other cases had sequelae, one was mentally defective and a severe epileptic, another was difficult to manage and had fits, a third had a slight hemiparesis, and a fourth was affected by sudden attacks of falling or stumbling.

The following Table shows the results according to type of case:

Type	Cases	Deaths	Complete Recovery	Survivors with Severe Disability
1	28	9 (32%)	13 (46·4%)	6 (31·6%)
2	15	1 (6·6%)	11 (73·4%)	
3	9	2 (22·2%)	3 (33·3%)	1 (14%)
4	17	2 (11·6%)	10 (58·8%)	3 (20%)
Others	24	1 (4·1%)	18 (75%)	5 (21·7%)
Total	93	15 (16%)	55 (59%)	15 (19%)

Summary

A study of 93 cases of encephalitis is presented; 65 (12 deaths) were of unknown aetiology and 28 (3 deaths) followed definite infections.

Sequelae were encountered in 23 of the 78 survivors, an incidence of almost 29%. They were severe or disabling (fits, mental reduction, or hemiplegia) in 15 cases, or 19% of the survivors.

An attempt has been made to group many of the cases according to the type of the clinical illness, and it has been found that there appears to be no constant relationship between the clinical picture and the aetiology or pathology. The histological changes in the brain have

often been surprisingly mild and have been disproportionate to the degree of cerebral disturbance seen during life.

It is suggested that, to some extent, the severity of the illness may be assessed by observing the mode of onset, the depth and duration of unconsciousness, the frequency of convulsions, and the persistence of signs indicating focal damage of the brain.

I am indebted to Professor Sir James Spence for much help and criticism in preparing this paper, and for allowing me to use many of the cases under his care. My thanks are due also to Dr. George Davison, Dr. F. J. W. Miller, Dr. S. D. M. Court, and Dr. C. E. Cooper for inviting me to see and to use the records of their cases.

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EXTRAMEDULLARY PLASMOCYTOMA

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Plasma-cell tumours may occur in bone and in soft tissues. Multiple myeloma is the most common manifestation, and its clinical and pathological features are well known. The solitary plasmocytoma of bone and extramedullary plasma-cell tumours are less common, while the interrelationship of the three conditions is still not finally proved. This case of extramedullary plasmocytoma is recorded because of its rarity, its unusual clinical presentation, and its interest as a case for differential diagnosis.

Case History

A man aged 55, who had lived in Jamaica all his life, was admitted to the Royal Infirmary, Sheffield, in August, 1952. In March, 1950, he had noticed a swelling on the left side of his neck. The following day he had a pyrexia of 102° F. (38.9° C.), and was treated by his doctor with penicillin injections. After a week the temperature subsided, but the swelling in his neck remained. The temperature rose again for several days in May, 1950. A radiograph of his chest and a full blood count at this time revealed only a "slight anaemia." His doctor diagnosed tuberculous glands of the neck. Thereafter, at intervals of six weeks, he had pyrexia, occasionally as high as 104° F. (40° C.), which persisted for several days before subsiding. In April, 1952, a lymph-node biopsy was reported on as Hodgkin's disease.

On examination three enlarged lymph nodes were present in the left anterior triangle of the neck. The largest of the three was approximately 2 cm. in diameter. They were freely mobile and painless. Examination of the oral cavity was normal and there was no evidence of dental caries. The nose, nasopharynx, pharynx, and larynx were examined by an otolaryngologist and pronounced normal. A complete clinical examination revealed no other abnormality.

Investigations.—*X*-ray examination of the chest, skull, lumbar spine, long bones, and accessory air sinuses revealed nothing abnormal. The Wassermann and Kahn reactions were negative. Agglutination reactions: *Brucella abortus* and *Brucella melitensis* less than 1/10. The urine was examined on many occasions: albumin was constantly present, but tests for Bence Jones proteose were repeatedly negative. Plasma protein: serum protein, 8.3 g. per 100 ml. (albumin 4 g., globulin 4.3 g.). Haematology: haemoglobin, 82%; red cells, 4,000,000; leucocytes, 7,000 (band cells 3%, lymphocytes 24%, polymorphs 64%, monocytes 6%, eosinophils 3%). The white-cell morphology appeared to be within normal limits. Platelets 620,000 per c.mm. (Lempert). Bone marrow (left ilium): The abnormal features included the presence of some macronormoblasts and an occasional megaloid cell. Abnormal nests of plasmocytes and their precursors were seen—in all, 5.6% of 500 cells. There was megakaryocytic hyperplasia.

Biopsy of the cervical lymph node on August 29 was reported on by Professor Willis as follows: "The extremely heavy infiltration of this lymph node by plasma cells is, I think, rather more than might be accounted for by any inflammatory disease, and my diagnosis is plasmocytoma. Whether this may be due to a primary growth in the upper respiratory passages or to skeletal myelomatosis can only be decided by other investigations, especially *x*-ray studies of the bone. The high plasma protein level favours myelomatosis. Bence Jones proteosuria should be carefully watched for."

The patient's general condition remained good and no further pyrexia occurred. As the radiological examination of the bones, the clinical state of the patient, and the other investigations were against a diagnosis of multiple myeloma, the lesion in the neck was treated with *x*-irradiation as a case of primary extramedullary plasmocytoma. Satisfactory regression of the remaining enlarged glands took place.

Since his return to Jamaica he has remained in good health. No Bence Jones proteosuria has been demonstrated. Radiological findings (skull, thorax, vertebral column, pelvis, long bones of upper and lower extremities) were normal in May, 1953.

Discussion

Solitary plasmocytoma is an established clinical condition. Although any part of the skeleton may be the site of such a lesion there appears to be a special predilection for the innominate bone and the long bones of the lower limbs. Amongst recorded cases are those of Rogers (1930), Chesterman (1936, 1948), Leedham-Green *et al.* (1938), Willis (1941), and Lumb (1948).

Willis (1941) considers that in order to establish a diagnosis of solitary plasmocytoma the following criteria must be fulfilled: microscopical proof that the tumour is of plasma-cell nature; exclusion of the possibility that the lesion is the first evidence of generalized myelomatosis; there must be radiological proof that no skeletal lesions are present, both at the time of examination and at subsequent examinations at repeated intervals; and Bence Jones proteosuria shall be absent on repeated examinations.

The validity of this last criterion is questioned by Lumb (1948), who found Bence Jones proteose in the urine of a case proved at necropsy to be one of solitary plasmocytoma of the sacrum. He concludes that the proteosuria is consequent on actual tumour volume—namely, the amount of bone-marrow involvement.

Plasmocytomas of soft tissue are much less often encountered. Hellwig (1943) found 127 published cases in the literature reviewed between 1905 and 1942, to which he added a case of his own. The lesions in most cases are situated in the upper air passages, especially the nasopharynx, maxillary antrum, and oral cavity. Cases have

also occurred in the conjunctivae, while odd sites recorded include the testis and uterus (Andersen, 1949) and pancreas (Hefferman, 1947).

The occurrence of extramedullary plasmocytoma in cervical lymph nodes unassociated with other lesions is referred to by Hellwig (1943) and by Andersen (1949). Andersen quotes a personal case, occurring in a submaxillary lymph node. Hellwig was able to find four cases, of which three subsequently developed lesions elsewhere. McNamara and Rogers (1943) recorded a case of extramedullary plasma-cell tumour of a tonsil with metastasis in a cervical lymph node, the interval between the removal of the primary lesion and the appearance of the metastasis being six years. In our case the lesion appears to be localized to a group of glands. A gland had previously been removed for biopsy elsewhere, and at the more recent biopsy a further complete gland was removed.

The possibility of a metastasis from a primary growth in the nasopharynx, antra, tonsils, etc., was considered. Radiological examination of the antra was negative, as was a complete clinical examination by an oto-laryngologist.

The late development of multiple myeloma in some cases of solitary plasmocytoma has led to certain conjectures regarding the pathogenesis of the two conditions. Some thought that the multiple lesions were due to a form of metastasis (Cutler *et al.*, 1936). Geschickter and Copeland (1928) found myeloma cells in marrow blood vessels, interpreting this finding as evidence of that possibility. Other authors, however, consider that the disease is multifocal in origin. The various forms of the disease, they say, should not be regarded as separate entities but as different manifestations of the same process (Lumb and Prosser, 1948; Lumb, 1948; Snapper, 1949). If this theory be accepted a solitary plasmocytoma must be regarded as a single focus of disease, which more usually presents in a multifocal form (Lumb, 1948). It is suggested by Willis, however, that as a plasmocytoma of the bone may remain solitary for years, and that, as a generalization, when it occurs it usually does so early, it is more probable that there are two separate types of the disease. He is of the opinion that "if thorough radiographic examination one year from the date of tentative diagnosis is unequivocally negative and proteosuria has been regularly absent, it is improbable that signs of generalized myelomatosis will appear later, and the tumour may be diagnosed with reasonable certainty as a solitary one."

Many cases of extra osseous deposits occurring in multiple myeloma have been recorded (Churg and Gordon, 1950; Hayes *et al.*, 1952). Any organ may be so implicated, but most commonly those of the extraosseous haemopoietic system—namely, spleen, lymph nodes, and liver. Churg and Gordon state that in their experience the more lymph nodes taken for section the more commonly is myelomatous infiltration found. The retroperitoneal nodes are involved most commonly, the hilar glands less frequently, superficial adenopathy being rare. In our case multiple myeloma was regarded as probably eliminated in view of the negative radiological findings and the absence of Bence Jones proteose. The marrow pictures were equivocal.

The history of attacks of high pyrexia was difficult to associate with a diagnosis of solitary or multiple myeloma. No abnormal pyrexia was noted during the patient's stay in hospital. Bailey and Haines (1951) found fever significant in only 1 to 3% of cases of multiple myeloma, and seldom was the temperature in excess of 100° F. (37.2° C.). Unfortunately, it was not possible to obtain the sections of the lymph-node biopsy reported on as Hodgkin's disease in April, 1952. The histological picture of Hodgkin's disease may be simulated by various kinds of chronic lymphadenitis, notably brucellosis, glandular fever, and torulosis. In view of the febrile history, it is possible that this biopsy may have shown a picture different from the latter one. Agglutination tests for brucellosis were negative.

The fact that albuminuria was present but Bence Jones proteose absent calls for cautious comment. Magnus-Levy (1932) (quoted by Bailey and Haines, 1951) thought that where these findings occurred the albuminuria was largely due to the Bence Jones fraction and that negative reports of its absence were erroneous. In Bailey and Haines's series of cases, 29 out of 32 patients suffering from multiple myeloma had albuminuria. This was equal to 90% of their cases, and was the most frequently observed positive laboratory investigation in their series.

More than a year has elapsed since the first biopsy was made in our case, and in view of the normal findings on recent radiological examination it is most likely that the lesion was a primary extramedullary plasmocytoma. Diffuse plasma-cell myelomatosis with little or no radiographic evidence of bone lesions does occur, and this is still a possibility in view of the equivocality of the marrow picture. The continued absence of Bence Jones proteosuria is, however, a strong point in favour of the former diagnosis.

Summary

A case of extramedullary plasmocytoma is reported. The differential diagnosis, the interrelationship of the three main types of plasma-cell tumours, and the significance of the main findings are discussed.

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The Tobacco Industry Research Committee in the U.S.A. has invited university, hospital, and other medical research organizations to submit proposals for specific cancer research projects for consideration by the committee's scientific advisory board. The board is said to be now reviewing 60 applications and inquiries already received. An initial fund of $500,000 has been appropriated for research. The Tobacco Industry Research Committee is composed of the large cigarette-manufacturers, tobacco-growers, and warehousemen. The scientific advisory board is guiding the development of long-term research to be conducted in institutions outside the tobacco industry. The industry will not set up any research facilities. No industry funds will be given to tobacco company laboratories. All projects will be in addition to research carried on by companies. The members of the advisory board are: Dr. CLARENCE C. LITTLE, director of the Roscoe B. Jackson Laboratory; Professor MCKEEN CATTELL, head of the department of pharmacology at Cornell University Medical College; Dr. LEON JACOBSON, professor of medicine at the University of Chicago; Dr. PAUL KOTIN, assistant professor of pathology at the University of Southern California Medical School; Dr. KENNETH LYNCH, professor of pathology at the Medical College of South Carolina; Dr. STANLEY P. REIMANN, scientific director of the Institute for Cancer Research, Philadelphia; and Dr. WILLIAM F. RIENHOFF, Jr., associate professor of surgery at the Johns Hopkins School of Medicine, Baltimore.

ISONIAZID AND WEIGHT GAIN

A PILOT INVESTIGATION

BY

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In groups of patients with pulmonary tuberculosis treated with isoniazid a remarkable gain in weight has been one of the principal effects reported (Medical Research Council, 1952, 1953). Compared with other treatments, weight gain has been so marked as to lead to a suspicion that a non-specific effect on metabolism was involved as well as a direct effect on the disease. There have also been reports of a great increase in appetite, undue sleepiness or wakefulness, and alterations in emotional tone, although none of these has been so frequent as the gain in weight. In order to determine whether it was worth while undertaking detailed metabolic investigations or a large-scale trial in normal subjects it was decided to carry out a controlled pilot trial on a small scale.

Methods

The subjects were eight male medical members of this department aged between 25 and 40. None had had tuberculosis, and in all a normal radiograph of the chest was obtained immediately before the start of the trial. They were divided by random allocation into a treatment group and a control group, each of four subjects. No subject knew to which group he had been allotted. The total period of the trial was fourteen weeks, including an initial observation period of two weeks before administration of any drugs and a final two-weeks period after administration had stopped. The control group received capsules containing lactose, and the treatment group was given isoniazid 100 mg. twice a day in identical capsules. The control group received lactose for the whole ten weeks. During the ten weeks of administration the treatment group received isoniazid for eight weeks and lactose for two weeks. By this plan each subject given isoniazid had control periods on lactose and on observation alone. In addition the whole treated group was compared with a control group, randomly selected, which received only lactose.

The subjects were weighed weekly to the nearest quarter-pound (0.1 kg.). In order to avoid suggestion or alteration in food intake they were weighed with their backs to the scale and were not informed of the readings. At the end of every week's treatment each subject filled in a questionary recording his impressions with regard to appetite, sleep, emotional tone, or any other possible effects of the drug.

Results

The weight changes are given in the Table. The individual gains or losses of weight over the two-weeks initial and two-weeks final observation periods are listed for both treatment and control groups. For the control group the weight change over the ten weeks on lactose is recorded, but for the treated group the changes during the two weeks on lactose and the eight weeks on isoniazid are given separately. The average weight change per man per week is calculated for each period. It will be seen that the average weight gain per man per week when the treated subjects were on isoniazid was 0.13 lb. (59 g.), compared with 0.12 lb. (54 g.) when on lactose and 0.53 lb. (240 g.) during the initial two-weeks observation period when no drug was administered. An average loss of 0.17 lb. (77 g.) occurred during the final two-weeks observation period, suggesting that there was no delayed effect of isoniazid in increasing weight. The control group averaged 0.25 lb. (110 g.) gain per man per week when on lactose and 0.22 (100 g.) and 0.36 lb. (160 g.) during the initial and final observation periods. The individual fluctuations in the two groups do not suggest that there was any difference between them attributable to the drug. It will be noted that both groups on average gained weight. This may be because the trial was started in January and continued to the early spring, or possibly because the trial itself had some psychological effect.

Weight Changes in Normal Males Given Isoniazid and in a Control Group

Subject	Loss or Gain in Weight (lb.)				
	2 Weeks' Initial Observation	2 Weeks on Lactose	8 Weeks on Isoniazid	2 Weeks' Final Observation	Net Change in 4 Weeks
Treatment group:					
T1	+1	−½	−3½	+1½	−1
T2*	+1½	+1	+3½	−2	+4½
T3	+1½	+½	+4	+½	+6½
T4	0	−½	−½	−1½	−2
Total	+4½	+1	+4	−1½	+7½
Average weight change per man per week (lb.)	+0·53	+0·12	+0·13	−0·17	+0·14
Control group:		10 Weeks on Lactose			
C1	−1	+2½		+5	+6½
C2†	−1	+6		−1	+4
C3	+2½	+½		−1½	+1½
C4	+1½	+1½		0	+2½
Total	+1½	+10		+2½	+14½
Average weight change per man per week (lb.)	+0·22	+0·25		+0·36	+0·26

* This subject stopped isoniazid after 6½ weeks because of Raynaud's phenomenon. The next weighing was at 7 weeks, so he is included in the calculations as if he had had 7 weeks' isoniazid and 3 weeks' subsequent observation.

† Weight for final observation week not recorded: calculations based on a single final observation week and 13 weeks' total observation.

Appetite.—Of the four subjects in the control group, two noted no change; the other two recorded fluctuations at varying periods. In the treatment group, only one recorded an unchanged appetite; fluctuations occurred in the other three, but without any consistent pattern which suggested an effect of the drug.

Sleep.—In the control group two observed no change, whereas two recorded variations in their sleep requirements from week to week. They were the same subjects who had shown some variations in their appetite. In the treatment group three recorded no change, but the fourth said that he was definitely more sleepy in the evenings during the last three weeks of the course, and during the last two weeks had been having more frequent nightmares. It is, to say the least, doubtful whether these changes should be attributed to isoniazid.

Emotional Tone.—One of the control group stated that he had become more cheerful, but in the treatment group no changes were recorded.

Other Possible Side-effects.—The only other effect which might be of significance was an experience of one subject to whom isoniazid was being administered. After four and a half weeks of continuous isoniazid treatment he experienced Raynaud's phenomenon in both hands, with stiffness, blanching, and coldness. This became steadily worse during the ensuing two weeks, and the drug was stopped. There was steady improvement thereafter. This subject had never experienced Raynaud's phenomenon before, but its relation to isoniazid must remain in doubt.

Discussion

The results of this study in man, although its scale was limited, are consistent with experiments in animals. Normal rats treated with isoniazid showed no significant gain in weight (Benson *et al.*, 1952; Rubin *et al.*, 1952), and in dogs there was no change in metabolic rate (Rubin and Burke, 1953). In man, Faloon (1953) found no change in nitrogen balance, appetite, or food intake in three patients with non-tuberculous disease given isoniazid for six to eight days. The observations here presented provide no evidence that isoniazid has any effect in causing gain in weight in the normal human male. In view of the negative results, we do not contemplate engaging in a trial on a larger scale. It seems doubtful whether the minor side-effects noted above were attributable to isoniazid.

Summary

The average weekly weight gain in four healthy males receiving isoniazid for eight weeks was similar to the gain in the same group treated for two weeks with control capsules containing lactose and to the gain during four weeks on observation alone. The average weekly gain was less than that of a similar group of four males treated for 10 weeks with control capsules containing lactose. We have therefore obtained no evidence to suggest that isoniazid in tuberculous patients has an effect on weight gain other than that due to its effect on the disease. No side-effects were recorded which could be attributed with certainty to isoniazid. One member of the treated group became unduly sleepy; another experienced Raynaud's phenomenon for the first time. One of the control group experienced an unexpected increase in cheerfulness, but no change in emotional tone was recorded by any member of the treated group.

We are most grateful to our colleagues who cheerfully put up with the inconveniences of the trial. We also record our gratitude to Messrs. E. R. Squibb and Sons for a generous gift of the isoniazid and control capsules. This investigation is one of a series supported by a grant from the Royal Victoria Hospital Tuberculosis Trust.

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The annual report of the Fountain Hospital, the 600-bedded hospital at Tooting Grove for mentally defective children from London and Surrey, draws attention to Section 3 of the Mental Deficiency Act, which allows a child to be placed in hospital by the parents without the need of a magistrate's order. Of the 84 certified direct admissions to the Fountain Hospital during 1953, over 80% were admitted under this procedure. The admission of young children without any legal formalities, the report continues, would go a long way towards improving the public's attitude to mental deficiency in young children. Indeed, a plea is made that this should be tried out experimentally. "If the Fountain Hospital, owing to its special circumstances, could be exempted for a temporary period from the normal working of the Mental Deficiency Acts experience would be gained in the *voluntary* care of defective children, comparable to that made possible by the Mental Treatment Act of 1930. This evidence might be of considerable value to the Royal Commission inquiring into the certification and detention of mental patients."

BLOOD GROUPS AND GYNAECOLOGICAL CANCER

BY

ERIK KROKFORS, Med.lic.

AND

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Stocks showed in 1950 that the standardized mortality of cancer of the stomach tended to be greater in northern than in southern towns in England. He assumed this to be connected with the fact that gastric cancer depends on an irritant. In an attempt to explain the variations in mortality, Aird, Bentall, and Roberts (1953) demonstrated that the frequency of blood group A was greater in patients suffering from gastric cancer than in the general population of the same locality. They collected their series from a number of hospitals in England and Scotland, using as controls an equal number of patients chosen at random from the same hospital or, where this was difficult, estimating an equal control number from the blood-group frequencies in large numbers of the local population. In most cases diagnosis was confirmed by a histological report; in only a few cases were the authors dependent on radiological findings or on the clinical picture alone.

Table I shows the results of Aird, Bentall, and Roberts. It indicates that in different parts of England and Scotland the frequency of blood group A was greater and that of blood group O correspondingly less in patients with cancer of the stomach than in the general population.

TABLE I

	Cancer Cases				Controls			
	O	A	B	AB	O	A	B	AB
Newcastle (101 cases)	43·6	43·6	11·9	1·0	52·5	37·4	7·6	2·5
Leeds (217 cases)	42·4	47·9	7·4	2·3	46·5	40·3	7·1	6·2
Manchester (771 cases)	44·7	44·5	6·4	3·8	52·1	38·4	7·0	2·5
Liverpool (217 cases)	39·2	44·7	12·4	3·7	49·7	39·6	7·8	2·7
Birmingham (100 cases)	37·0	57·0	3·0	3·0	49·6	44·4	3·0	3·0
Total of Northern England (1,406 cases)	42·9	46·4	7·6	3·1	50·7	39·3	6·8	3·2
London (1,340 cases)	43·1	46·0	7·9	2·9	45·8	42·2	8·9	3·1
Scotland (478 cases)	51·2	36·4	9·6	2·7	52·6	32·5	11·7	3·1
Overall figures (3,632 cases)	44·5	44·8	7·8	2·9	48·6	39·8	8·3	3·2

Our Own Investigations

It seemed of interest to make a corresponding study of the distribution of the blood groups in patients suffering from gynaecological cancer. Our series consists of 300 patients with uterine or other gynaecological cancer whose blood groups had been determined; they were treated at the Women's Clinic of the University of Helsinki during the period 1948–53. Diagnosis was confirmed in all cases by a histological report. Owing to the centralization of hospital conditions in Finland, the majority of all cases of gynaecological carcinoma, both operative cases and those given radiation, are treated at the Women's Clinic in Helsinki. This being so, the patients no doubt represent a cross-section of the population as regards distribution of blood groups. The control series was therefore selected on a similar basis.

All such acute cases of gynaecological disease as are predominantly from Helsinki or its immediate vicinity—for example, abortions and extrauterine pregnancies—were excluded. We also used for control purposes the data published by Streng and Ryti (1927) regarding blood-group distribution in the general population of Finland.

Table II compares our results with the data obtained by Streng and Ryti.

TABLE II

	Gynaecological Cancer				Controls			
	O	A	B	AB	O	A	B	AB
Krokfors and Kinnunen	113 37·7%	110 36·7%	57 19%	20 6·7%	98 31·6%	139 44·8%	48 15·5%	25 8·1%
Streng and Ryti					33·5%	42·7%	16·8%	7·0%

Comparison of the control data in Tables I and II shows, first, that the frequency of blood group O is considerably less and that of groups B and AB correspondingly greater in the general population of Finland than in that of England and Scotland. Group A is about equally frequent in both countries. But when we compare the distribution of blood groups in our carcinoma patients and in our controls we find that blood group O seems to predominate clearly in the cancer group, blood group A having a correspondingly lower frequency.

We subclassified our cancer group into cancer of the uterus and other gynaecological cancer, and this seemed to cause no appreciable changes in the distribution of the blood groups (Table III).

TABLE III

	O	A	B	AB
Cancer of the uterus ..	37·9%	37·1%	18·5%	6·5%
Other gynaecological cancer	36·5%	36·5%	20·0%	7·0%

It occurred to us that there might be a correlation between the blood group and the age of the patient at the onset of gynaecological cancer. We therefore studied separately 100 patients, the youngest in the series. Their upper age limit was 45 years. The blood groups were as follows: O, 42%; A, 33%; B, 17%; and AB, 8%. The relatively greater frequency of blood group O thus seemed to increase further when this subdivision was made.

Conclusion

On the basis of our own studies we can only state briefly that, in contrast to the English series of cancer of the stomach, a Finnish series of gynaecological cancer showed a clearly lower frequency of blood group A than the corresponding controls. It seemed, on the contrary, that the incidence of blood group O was particularly high in our series of gynaecological cancer; this appeared most distinctly in the youngest patients studied.

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From May 16 margarine must contain between 760 and 940 international units of vitamin A per ounce and between 80 and 100 international units of vitamin D per ounce. This vitamin-A content is roughly equivalent to that of butter. This Order applies to all home-produced and imported margarine sold by retail, including margarine sold as such by a caterer but not margarine used by him in made-up foods or in cooking. It does not apply to sales of margarine to a caterer.

Medical Memoranda

Extreme Sensitivity to Insulin

Since its introduction by Sakel in 1935, treatment by insulin has been widely used in various forms of mental illness. Considerable variations have been experienced in the reaction of patients to insulin, and it is generally agreed that there is marked individual sensitivity to the drug (Tennent, 1944). Success in the induction of coma has been reported with doses of 15 units (James *et al.*, 1938) and of 18 units (Parfitt, 1937). A case is described in which coma was induced with a dose of 2 units, and a method of desensitization is given. I have been unable to trace any record in the literature of coma being induced with such a small amount of insulin.

CASE REPORT

An unmarried woman aged 19 suffering from anorexia nervosa was referred to Fulbourn Hospital, Cambridge, for a course of modified insulin on July 20, 1953. Her weight at this time was 5 st. 7¼ lb. (35 kg.).

The initial dose (see Table I) was 15 units, given intramuscularly at 7.15 a.m. At 9.30 a.m. she was in sopor and showed loss of a normal response to speech and

TABLE I

Days	Units of Insulin Given at 7.15 a.m.	Time of Sopor	Time of Coma
1	15	9.30 a.m.	10.5 a.m.
2	10	9.50 „	10.0 „
3	1	No reaction	No reaction
4	3	10.15 a.m.	10.25 a.m.
5	Sterile water	No reaction	No reaction
6	2	10.0 a.m.	10.30 a.m.

impairment of orientation. At 10.5 a.m. she was in coma; she showed loss of all purposive responses, none being elicited from visual, auditory, or tactile stimuli. The next day the dose was reduced to 10 units, and sopor was produced at 9.50 a.m. and coma at 10 a.m. Because of this marked sensitivity, the following morning she received only 1 unit. This produced no effect. The next day the amount of insulin was raised to 3 units, and sopor came on at 10.15 a.m. and coma at 10.25 a.m.

To ensure that it was in fact the insulin which was causing these reactions, on the succeeding morning an intramuscular injection of sterile water was given at 7.15 a.m., but this had no effect whatever on the patient. At the same time a specimen of blood was taken in order to ascertain the fasting blood sugar. This was 0.72 g. per 100 ml. The next morning 2 units of insulin was given, and this time sopor was induced at 10 a.m. and coma at 10.30 a.m.

It was decided to attempt to desensitize the patient by starting at a dose of 0.2 unit and increasing this by 0.2 unit daily. This proved successful, and by December 18 she was having 17 units daily, which was enough to induce drowsiness but not to produce sopor or coma. Her weight was then 6 st. 2 lb. (39 kg.).

COMMENT

It is known that insulin hypersensitivity is present in clinical cases of hypopituitarism—for example, Simmonds's disease (Wright, 1952). As the physical picture of this disease may closely resemble the classical "anorexia nervosa" and as there may be a secondary disturbance of pituitary function in the later and more severe stages of anorexia nervosa, the patient was investigated to discover if any pituitary dysfunction was present. The following factors were in favour of anorexia nervosa: she was a young unmarried woman of a neurotic obsessional personality, there was no loss of hair, and, in spite of emaciation, restless overactivity was very obvious.

Fraser and Smith (1941) have sought to differentiate between organic pan-hypopituitarism and "functional" anorexia nervosa by estimation of 17-ketosteroids and an insulin-tolerance test. In the organic disorder they found

extremely low or no excretion of 17-ketosteroids, and after injection of insulin under controlled conditions delay of blood sugar in returning to normal. The 17-ketosteroid output was often low in anorexia nervosa, but in no case entirely absent. Although neither test is specific, they believe that the combination of both enables a diagnosis of pan-hypopituitarism to be made with fair accuracy (Hemphill, 1944). In the above case the 17-ketosteroid excretion was 5.8 mg. a day (normal range, 4–20 mg. a day). The insulin-tolerance test showed no delay in the return of the blood sugar to normal after 120 minutes (see Table II). It would therefore seem that the pituitary was functioning normally.

TABLE II.—*Insulin-tolerance Test* (0.3 *Unit per kg. Body Weight Given Intravenously at* 7.15 *a.m.*)

Blood Taken	Result (g./100 ml.)
Before insulin given	0·077
20 minutes after giving insulin	0·056
30 " " " "	0·047
45 " " " "	0·059
60 " " " "	0·057
90 " " " "	0·065
120 " " " "	0·077

I would like to thank Dr. D. H. Clark, medical superintendent of Fulbourn Hospital, for his valuable criticism of this report.

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Poliomyelitis in Mother and Child in Trieste

In recent years we have begun to recognize that poliomyelitis in infancy is not a rare occurrence. Reports by earlier observers, including Mouton, Smillie, and Bowers (1950), have stressed the rarity of infection in young children, but in recent reports such as that of Logan (1952) a different story is told. He records that in the outbreak in England and Wales of 1950 there were, for example, 82 reported cases in children under 6 months of age.

Infection in the neonatal period, however, although well known, is an event of some interest. Thus there are reports of five cases in 1950 in England and Wales in such an age group, of which four were fatal. In 1952 an outbreak occurred in a private nursing-home (Sims-Roberts and Thomson, 1953), and of the four babies affected three died. Wright and Owen (1952) record a further case of neonatal infection in which both mother and child died of the disease. This therefore brings the total of neonatal cases in England and Wales in 1952 to five, with four fatalities. Obviously the incidence is much greater than these figures would suggest, as subclinical and non-paralytic cases are more common than paralytic and more difficult to detect in the very young child. Indeed, it is usually the onset of paralysis which is the first indication that infection has taken place, and the pre-paralytic stages are very often silent. Thus in two outbreaks in England in 1950 and 1952 affecting many thousands of people there are reports of only 10 neonatal cases, of which 8 were fatal.

In Trieste there is an Italian–Slav population of approximately 300,000, and a British military population of 5,500, including troops and families. Only 14 cases of clinical poliomyelitis were reported here last year, and in the British military population only two. These two cases were in a mother and her newborn child, and are of interest because of the rarity of such an event, considering the total number of cases involved. No cases have been recorded by the American forces in Trieste.

Neonatal infection is rare and often fatal, but for some obscure reason infection in both mother and young child seems to be even less frequent. In Logan's figures for 1950 there were, according to Geffen and Tracy (1953), only six instances of infection in mother and child, and of these only two of the babies were in the neonatal period when affected. The ages of the other children in whom there was this "mother–child" infection varied from 9 to 17 weeks.

Thus in 1950 there were only two cases in which clinical or subclinical poliomyelitis was recognized in both mother and newborn child. In 1952 only one case was recorded—that of Wright and Owen, in which both mother and child were affected—although in one case reported from the nursing-home outbreak poliomyelitis virus type III was isolated from the stools of one healthy mother. There are examples of only three cases of double infection in these two years, and it is of note that in all three cases the mother died, and in two the child died also. The remaining child was said to have suffered from a severe attack of the disease. The following cases are therefore of interest in that they record the occurrence of a "mother–child" infection in a very small poliomyelitis outbreak affecting a British population overseas. Further, both mother and child have survived and at the time of writing this report were improving.

CASE HISTORIES

1. The wife of a British Army sergeant was admitted to the B.M.H., Trieste, on September 13, 1953. Thirteen days previously she had been delivered of a healthy female infant in the same institution. When seen on September 12 she had complained of two days' headache and fever, and on the morning of admission she noticed weakness of both legs and inability to pass urine. On examination she was pyrexial, temperature 103° F. (39.4° C.), and there were signs of complete flaccid paralysis of the lower limbs without sensory changes, together with bladder and bowel paresis. Lumbar puncture on September 14 showed 234 cells per c.mm., 87% of which were polymorphs; and 75 mg. of protein per 100 ml.

2. The daughter of the above patient was admitted at the same time as her mother and isolated from her. She was then 13 days old, and it was noted that her rectal temperature was 101° F. (38.3° C.). One day later the child was still pyrexial, and suddenly developed a complete and flaccid paralysis of the right arm with minimal involvement of the muscles of the left shoulder girdle also. The general hypotonicity and drowsiness of the child were significant features during and immediately after the development of paralysis. These characteristics have been stressed by Shelokov and Weinstein (1951), the classical signs and symptoms of poliomyelitis in its early stages often being absent at this age. Lumbar puncture on September 16 showed 69 cells per c.mm. (17% polymorphs, 72% lymphocytes), and 110 mg. of protein per 100 ml.

After four weeks' observation both of these patients were transferred to another centre for further treatment. At this time their clinical condition had improved and some movement was beginning to return in the lower limbs of the mother.

SUMMARY AND CONCLUSION

Two cases of poliomyelitis are reported in the Army population in Trieste, where a very small outbreak occurred.

These two cases consisted of a mother and her 13-days-old child, both of whom sustained paralysis and had typical cerebrospinal fluid.

The reported combination of clinical infection in mother and newborn child is rare, and that of poliomyelitis in the neonatal period is also of sufficient rarity to record.

Both of these patients have survived, which is of interest in that poliomyelitis in the neonatal period is often fatal to the infant and, indeed, to the mother when affected.

My thanks are due to Lieutenant-Colonel R. H. Hunt for permission to publish these cases.

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Reviews

THE SCIENCE OF PATHOLOGY

Lectures on General Pathology. Edited by Sir Howard Florey, M.D., F.R.C.P., F.R.S. (Pp. 733; 343 illustrations and 4 coloured plates. 63s.) London: Lloyd-Luke (Medical Books) Ltd. 1954.

This volume, edited by Sir Howard Florey, is a collection of 37 lectures delivered at the Sir William Dunn School of Pathology, University of Oxford. They form part of a 16-weeks course in general pathology taken by students who have spent the previous year reading Honour School of Physiology and are about to begin their clinical training. Each lecture occupies between 10 and 20 pages of text and there are 10 contributors. The volume is profusely illustrated by original photomicrographs, many of which are taken from the published research work of the authors.

The editor is responsible for 10 lectures; Professor G. R. Cameron, of University College, London, for four and part of another, and Dr. G. P. Gladstone, the University Reader in Bacteriology, for five and part of three others. Each contributor deals with subjects in which he has a special interest. Dr. A. H. T. Robb-Smith, the Nuffield Reader in Pathology, discusses collagen; Dr. R. G. Macfarlane, the University Lecturer in Haematology, the reaction of the blood and blood-forming organs to injury; and Dr. F. K. Saunders, a member of the external staff of the Medical Research Council, the cellular and tissue reactions to viruses. Equally fundamental problems are reviewed in the form of reported lectures given as part of the course by Drs. E. P. Abraham and W. E. van Heyningen, who are senior research officers, and Drs. K. B. Roberts and H. Harris, who are scholars in the Sir William Dunn School. It is quite clear from the high standard of these lectures that the Oxford medical undergraduate is given an exceptionally good opportunity in the seclusion of his University to get a firm grasp of the general principles of pathology before he enters the strange and confusing atmosphere of his hospital.

It is surprising that British pathologists have been so reluctant to provide the serious student with a full and authoritative account of the general principles of pathology. This may be partly responsible for the fact that the educational value placed upon this subject shows such wide variations from one university to another, yet no one would deny that general pathology ranks as an experimental science in its own right and deals with a branch of biological knowledge which is an essential prerequisite for the proper understanding of clinical subjects. It is certainly difficult to teach general pathology during the clinical years, for there are too many legitimate distractions in the clinical atmosphere for teacher as well as student. This, however, does not account for the wide variation in the scope and quality of its teaching. The fact is that this fundamental science is in great danger of becoming eclipsed by the enormous accumulations of knowledge which deal with the practical application of its principles to clinical diagnosis, and it is to be hoped that Sir Howard Florey's book will check this ominous threat to one of the most basic of the medical sciences.

The last British treatise confined to general pathology and written by a panel of experts was published in 1913 under the editorship of M. S. Pembrey and James Ritchie. It was greatly treasured by a former generation of pathologists, but is now outmoded and out of print. It is therefore most gratifying to find, after a gap of 40 years, that Pembrey and Ritchie now has, in this product of the Oxford school, a modern equivalent and a worthy successor which preaches the same sound doctrine and is based upon the deep conviction that "the student must try to grasp what is known of the general principles underlying the pathological changes that he will be called upon to diagnose and treat."

As one might have predicted before reading the book, the editor is a strong and convincing advocate for the use of the experimental method, not only in pathology but with greater force in its clinical applications. He expresses the hope that "some students will find sufficient stimulus from the lectures to carry an experimental outlook into clinical medicine and surgery, for these subjects have suffered and continue to suffer in this country from an approach which pays too little attention to experimental science. At the present day nearly all significant advances in diagnosis, treatment, and prevention of disease depend upon the application of experimental methods."

For the most part the lectures deal with the various aspects of the "reaction to injury," using this word in its widest connotation. Inflammation, phagocytosis, haemostasis, fever, the tissue reaction to infective agents and to injuries inflicted by irradiation occupy over 40% of the text, while the general principles of immunity, the pathogenesis and virulence of micro-organisms, anaphylaxis, and specific hypersensitivity take up another 30%. Shock, haemorrhage, and oedema absorb 6%; healing and regeneration about 12%.

In a book devoting nine-tenths of its text to the reaction to injury it may be regarded as an unfortunate omission that the profound general metabolic response to injury receives so little consideration; but any criticism based on omission carries little weight, as the book was not planned to cover the whole subject, and in full compensation for its incompleteness it has two outstanding merits: first, that every lecture covers its subject in a commendably comprehensive manner which would be impossible in a textbook; second, that in almost all the lectures the author is dealing with a subject to the experimental study of which he has devoted a part of his life. One therefore finds, in dealing with such subjects as the participation of the lymphatics in inflammation, the secretion of mucus and inflammation in mucous membranes, blood coagulation and haemostasis, shock, regeneration, and the pathogenic action of bacteria, that the lectures have the indelible stamp of authority and are far more satisfying and infinitely more stimulating than the chapters of the average textbook. Almost every lecture is a model of the way in which scientific evidence should be handled and evaluated.

The inclusion of such general subjects as the pathology of growth and tumour formation, the functional failure of vital organs, the consequences of arterial ischaemia, and a number of other similar topics would have increased the bulk of the volume to unwieldy proportions. Having successfully but only partially filled so large a gap in British pathological literature, Sir Howard Florey and his colleagues, it is to be hoped, will regard it as a public duty to publish another volume of lectures—and the sooner the better.

GEOFFREY HADFIELD.

ADVANCES IN PAEDIATRICS

Advances in Pediatrics. Edited by S. Z. Levine. Associate Editors: John A. Anderson, Margaret Dann, L. Emmett, jun., A. Ashley Weech, Myron E. Wegman. Volume 6. (Pp. 323; illustrated. 58s.) Chicago: The Year Book Publishers Inc. London: Interscience Publishers Ltd. 1953.

This book, comprising seven monographs by recognized authorities, is well up to the high standard set by previous volumes in the series. Each article presents an up-to-date review of the subject and ends with a valuable list of references. Neonatal problems are very much to the fore at present, and this is reflected in the four monographs on, respectively, preventive prenatal paediatrics, intestinal obstruction in the neonatal period, haemolytic disease of the newborn, and pulmonary pathology in the newborn. Of these, perhaps the most stimulating is the first, by T. H. Ingalls, because he indicates the methods to be adopted if fresh light is to be thrown on the subject. As he points out, each approach—clinical, experimental, and epidemiological—presents its own difficulties, and the author's pen-picture of the clinician's feeling of frustration is worth quoting: "The nearly insurmountable obstacle to clinical study of prenatal sickness arises in the fact that the patient voices no complaint, remembers nothing about

his illness, hides himself from view, and puts off his visit to the doctor until the last possible moment."

S. van Crefeld's monograph on the lipoidoses is an excellent survey of a difficult subject; and the chapter by H. W. Dargeon on lymphosarcoma in childhood will be welcomed not only for its detailed information about a relatively uncommon growth but because the prognosis is viewed somewhat more hopefully than in the past.

The final monograph—on megaloblastic anaemia of infancy—is a comprehensive review of some 55 pages and with 122 references. The authors (W. W. Zuelzer and J. Rutzky) cover all aspects of this curious disorder and discuss their own cases in some detail. Prevention and treatment are carefully considered, and, as might be expected, the paper is a happy combination of the experimental and clinical viewpoints.

Each new volume of *Advances in Pediatrics* adds emphasis to the wisdom of having this series available in medical libraries.

NORMAN B. CAPON.

MYOCARDIAL CONTRACTION

On the Nature of the Myocardial Contraction: A Study of the Electrolytes. By F. Lenzi and A. Caniggia. Preface by Professor G. Izar. (Pp. 112; 19 figures. No price.) Basle and New York: S. Karger. 1953.

This little book describes the clinical application of the work of one of the authors on the electrolytes in the heart. The English is good and the book is most readable; even if the technical nature of the subject sometimes makes the expression rather hard to follow, there is really no great difficulty, for clarity and brevity are qualities to be found throughout. This subject is becoming of considerable importance to the cardiologist. The question of sodium metabolism is much to the fore. It seems likely that study of the electrolytes and the part they play in the contraction of the heart may provide the next big step forward in understanding what happens when the heart fails. The relative importance of the electrolytes and of adenosine triphosphoric acid is carefully discussed. It is with the former that most of the authors' work has been done. By using the terms of electrocardiography the authors have now sought to explain what goes on at the cell membrane. This gives some information about the variations of the concentration of ions inside and outside the cell. The opposition of the ions of sodium and potassium, the one mainly outside and the other mainly inside, affects the muscular contraction. They point out how particularly important is the "gradient" or actual differences in the levels of concentration of the ions across the cell membrane. How far the authors' theories are correct the clinician cannot judge, but it has been most interesting and stimulating to read about them. This book will certainly appeal to cardiologists as a good discussion of a fascinating subject which deserves careful study.

TERENCE EAST.

CANCER RESEARCH

Advances in Cancer Research. Volume 1. Edited by Jesse P. Greenstein and Alexander Haddow. (Pp. 590. $12.) London and New York: Academic Press Inc. 1953.

The post-war years have been noted for a series of excellent summaries on various subjects in biochemistry. These have appeared on both sides of the Atlantic, and in the case of the volume at present under review many have been prepared on both sides of the ocean. *Advances in Cancer Research* is edited by Professor J. P. Greenstein and Professor A. Haddow, both well-known names in the field. This volume is the first of a series which will be produced from time to time, and the object is to provide an up-to-date account of various aspects of cancer research. That this has been done can very readily be verified by turning to the references, and one will see that there are a number of papers quoted in late 1952.

The book begins with a very able summary of the present position in relation to electronic configuration in carcinogenesis by C. A. Coulson. The second part deals with epidermal carcinogenesis by E. V. Cowdry, and it is interesting in that the section is devoted to the question of epidermal carcinogenesis in the human subject. The milk agent is given a special section by Dmochowski, in which he gives a clear account of the rather complicated relationship of the milk agent and the hormonal production of cancer of the breast. W. U. Gardner gives a very full account of hormones in relation to the development of tumours in experimental animals, whilst R. J. C. Harris deals with the question of the Rous agent. This section concludes with an interesting speculative account on the origin of the Rous agent. Radioisotopes in relation to experimental cancer research are dealt with by C. Heidelberger, and a full summary of the present position of the carcinogenic aminoazo dyes has been written by J. A. Miller and E. C. Miller. The cytotoxic agents are discussed by W. C. J. Ross, and there is a most interesting account on nutrition in relation to malignant disease by A. Tannenbaum and H. Silverstone. There are some interesting observations recorded on cancer in man in relation to nutritional states. The volume concludes with a paper on plasma proteins by R. J. Winzler.

It is not possible to do more than mention the sections in this brief review, but in general it may be said that the standard of the whole book is very high indeed, and no cancer research laboratory can afford to be without it.

E. C. DODDS.

AGE AND ACHIEVEMENT

Age and Achievement. By Harvey C. Lehman. Memoirs of the American Philosophical Society held at Philadelphia for promoting useful knowledge. Volume 33. Foreword by Lewis M. Terman. (Pp. 359; 170 figures. 60s. or $7.50.) Princeton, U.S.A.: Princeton University Press. London: Geoffrey Cumberlege. 1953.

Osler's severe judgment that the world could do without men over 40 and would be well rid of men over 60 is unlikely to appeal to a generation more concerned with raising the pensionable age than with lowering the age at death. Nevertheless, for anyone above or near the age of 40 it will be comforting to learn that the contemporary viewpoint is supported by something more than humanitarian considerations. This comfort is provided in a book by an American professor of psychology who has attempted to identify the "great works" (in science, medicine, philosophy, music, art, and literature), and to establish the ages at which they were produced. His data indicate that although the age of greatest output is undoubtedly below 40, and is surprisingly constant over a wide range of subjects, there is no age at which men cease to make important contributions. Chloroform at 60 (the newspapers' interpretation of Osler's remark) or even at 80 would remove some useful as well as many useless people.

After inspecting the 61 tables and 170 figures in *Age and Achievement* the reader may ask himself whether it was necessary for the author to put himself to quite so much trouble to make his points. It is an unfortunate practice among social scientists to expand to book length material which in other fields would be communicated in a modest paper in a research journal, and one feels that Mr. Lehman might have had a greater reward for less effort if instead of examining age of achievement so exhaustively he had taken up one or more of the numerous problems raised by his fascinating subject. Nevertheless some of his data are interesting, although those who doubt the relevance of statistics to the human situation are unlikely to be reassured by the statement that "appropriate computations suggest that if an author is destined to produce a book of such unusual merit as to be chosen by 8 or more compilers of best book lists, the chances are much less than one to a thousand that the author will publish that book when he is beyond 80 years of age." And they may feel that one place of decimals would have been sufficient to convey the information that at the time he published the second part of *Faust* Goethe was 3.56 standard deviations above the mean age of 101 authors of 224 best books.

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CARDIAC SURGERY AND THE ARTIFICIAL HEART

Many successful experiments have now been performed at various centres throughout the world in which a mechanical device is substituted for, or assists, the heart and lungs of an animal. A temporary artificial circulation of this sort has now been used in several human patients. Elsewhere in this issue of the *Journal* Professor Ian Aird and his colleagues describe the use of a pump-oxygenator during an operation for the relief of aortic stenosis. The apparatus used was the one described last year in this *Journal* by Melrose,[1] who with his colleagues reported experiments on dogs.[2] F. G. Dodrill, of Detroit,[3] has recently reported four operations, using a mechanical heart.

The potential usefulness of such machines lies not only in cardiac surgery but also in the emergency treatment of acute cardio-respiratory failure. The apparatus consists essentially of a pump or pumps and of an oxygenator; the latter need not be used if the subject's lungs continue to function. Its purpose is to assist the heart, or to replace it entirely, or to replace one or other side of the heart. In reversible acute cardiac failure, as sometimes occurs with myocardial infarction, it should be possible to aid the enfeebled heart by withdrawing blood from the great veins, pumping it through the oxygenator, and returning it to the systemic circulation. The necessary cannulation of a major artery may mean its subsequent ligation is unavoidable. For cardiac operations a by-pass of one side alone will often suffice.

Since no efficient cardioscope has been devised, all operations on the heart valves must at present be done blindly, and guidance by the surgeon's sense of touch may often only be indirect, through instruments. The prospects of a dry heart offer attractive possibilities of operating under direct vision. To by-pass the right side of the heart blood must be withdrawn from the right atrium and returned to the pulmonary artery. Alternatively blood can be taken from the venae cavae, which are then clamped near the heart; but this manœuvre allows the considerable blood flow from the coronary sinus and Thebesian veins to enter the heart, which is then by no means dry. The cannula returning the blood to the circulation can conveniently be inserted in the lower branch of the right pulmonary artery pointing upwards, so that the left lung is also supplied. There are not many conditions for which the right by-pass is needed: perhaps the most important is congenital pulmonary stenosis; the septum must of course be intact and the main pulmonary artery clamped just below its bifurcation. It has been shown in animals, and the finding probably applies to man, that reflexes arise from the right side of the heart which pass by the vagus nerve and help to control the systemic blood pressure; as the atrium empties, the pressure falls. This effect is increased in the presence of anoxia, which underlines the importance of good oxygenation.

The left side of the heart can be by-passed by extracting blood from the pulmonary veins—four cannulae being used—and returning it to the aorta via the subclavian artery. This enables the mitral valve to be exposed under direct vision. The aortic valve must be competent or reflux of blood will flood the field. There are good prospects here for advance on the crude surgery now possible, and hope that an effective technique for the relief of mitral incompetence may be devised. The left side can also be by-passed by extracting blood from the left atrium; if this is done the atrium must not be left open, since air embolism will occur. This prevents exposure of the mitral valve, but prolonged blind manipulations can be done. By a combination of the methods described above both sides of the heart can be completely by-passed without using an artificial oxygenator—an arrangement probably of most value in the treatment of congenital defects with a patent septum. Professor Aird and his colleagues used the pump-oxygenator to assist the whole circulation, extracting blood from the inferior vena cava via the femoral vein and returning it to the aorta via the femoral artery after it had been oxygenated. The patient, with aortic stenosis, severe angina, and congestive failure, would not have been fit for operation without assistance, especially as the necessary manipulation would have reduced the coronary blood flow below the tolerable level, resulting in irreversible ventricular fibrillation. A successful dilatation was carried out. To prevent blood clot-

[1] *British Medical Journal*, 1953, **2**, 57.
[2] Ibid., 1953, **2**, 62.
[3] *J. Amer. med. Ass.*, 1954, **154**, 299.
[4] *J. thorac. Surg.*, 1953, **26**, 584.
[5] Dodrill, F. D., *et al.*, *J. Amer. med. Ass.*, 1952, **150**, 642.
[6] *Ann. Surg.*, 1951, **134**, 709.
[7] *J. thorac. Surg.*, 1953, **26**, 617.
[8] *Bull. Johns Hopk. Hosp.*, 1952, **90**, 131.
[9] *New York Times*, May 1, 1954.

ting in the apparatus heparin was added; in spite of neutralization by protamine, troublesome but not serious haemorrhage occurred towards the end of the operation. It was thought that this was mainly due to loss of platelets. The patient's angina was relieved, and her exercise tolerance greatly increased.

Dodrill and his colleagues[3,4] by-passed the right heart in a young man for twenty-five minutes, and performed a pulmonary valvuloplasty under direct vision; the patient made a complete recovery. In another case, a left by-pass enabled an open operation to be successfully performed on the mitral valve. A left by-pass for a closed mitral operation lasting seventeen minutes had previously been reported.[5]

Dodrill also describes an operation for congenital pulmonary stenosis on a girl who had both sides of her heart by-passed: she survived four days. The use of a mechanical heart during operation for the repair of cardiac defects has also been reported by Dennis and his colleagues[6] (successful repair of an atrial septal defect), by Helmsworth and his colleagues[7] (repair of ventricular septal defect, with death sixteen hours later), and by Dogliotti.[8] Operations have also been reported[9] to have been carried out successfully on the hearts of patients with the aid of a compatible donor's lungs instead of an oxygenator. The subjects' venous and arterial circulations are connected to those of the donor by polythene tubing; a pump assists the cross-circulation.

Hypothermia, or artificial lowering of the body temperature, by reducing the demands for oxygen allows a greatly reduced circulation and provides another means of obtaining a dry heart for the surgeon—perhaps by a less complicated method than the mechanical heart. It may be found that a combination of the two techniques will be valuable.

ALDOSTERONE, THE NEW ADRENAL STEROID

Some months ago we referred[1] to a new and highly potent adrenal steroid, provisionally termed electrocortin, which was isolated in crystalline form from the adrenal glands by British and Swiss investigators working in collaboration—Simpson and Tait, of the Middlesex Hospital, London, Reichstein and von Euw, of Basle University, and Wettstein and Neher, of the Ciba research laboratories, Basle.[2] These same workers[3] have now succeeded in establishing the chemical structure of the hormone, which chemically is closely related to cortisone and deoxycortone but differs in containing an aldehyde group. In view of this the new hormone has been named "aldosterone" instead of "electrocortin." Drs. C. L. Cope and J. Garcia-Llaurado draw attention in this issue of the *Journal* to reports of the occurrence of a sodium-retaining substance in normal human urine and of an increased amount of this principle in the urine in conditions such as congestive heart failure, nephrosis, and hepatic cirrhosis with ascites. It is of interest that Cope and Llaurado think it likely that the sodium-retaining effects observed by these earlier investigators were due to the presence in the extracts of aldosterone, for by means of paper chromatography they have identified what appears to be this hormone in certain urinary extracts which they found to have sodium-retaining activity.

So far detailed investigation of the physiological activity of aldosterone has been difficult because of the very small quantities that are obtained by extraction of the adrenal glands. In a recent paper Gross and Gysel,[4] of the Ciba laboratories, have reported experiments on the action of aldosterone in the adrenalectomized dog, the tests used being the survival test and the effect on the electrolyte and water metabolism. They found that the daily dose of aldosterone necessary for the maintenance of life in the adrenalectomized dog is 1.5 to 2.0 μg./kg. injected subcutaneously in two divided doses in oily solution, whereas the maintenance dose of deoxycortone acetate (D.C.A.) for animals weighing 13 to 16 kg. is 0.7 to 1.0 mg. injected subcutaneously daily. Aldosterone is thus 25 to 30 times more active than D.C.A. in this test. After changing over from D.C.A. to aldosterone, which owing to limited supplies could not be administered for more than ten days, the excretion of urine was increased and the urinary sodium and chloride showed a transient rise, while the concentrations of chloride, sodium, and potassium in the plasma showed no clear-cut changes. The authors suggest that the increased excretion was probably due to excretion of depots of sodium, chloride, and water which had been retained under D.C.A. therapy. These changes were accompanied by an increase in the haemoglobin concentration and in the blood non-protein-nitrogen, representing the disappearance of the hydraemia which develops in the adrenalectomized dog treated with D.C.A. In water-load experiments Gross and Gysel found that with aldosterone the excretion is delayed in about the same manner as with D.C.A., whereas, in contrast to D.C.A., overdosage with aldosterone for several days does not produce any marked retention of water, sodium, and chloride.

[1] *British Medical Journal*, 1953, **2**, 552.
[2] *Experientia (Basel)*, 1953, **9**, 33.
[3] Ibid., 1954, **10**, 132.
[4] *Acta endocr. (Kbh.)*, 1954, **15**, 199.
[5] *Schweiz. med. Wschr.*, 1954, **84**, 407.

On the clinical side Mach and his colleagues[5] have given aldosterone to two patients with Addison's disease and obtained results similar to those described above in the adrenalectomized dog. The effective dosage lay between 150 and 200 μg. per day (2.5–3.3 μg./kg.), aldosterone thus proving in man to be 20 to 30 times more potent than D.C.A. Within several hours of the beginning of treatment the clinical symptoms of the disease disappeared and within a few days skin pigmentation regressed and the blood pressure rose to normal. Like D.C.A., aldosterone caused sodium and chloride retention and increased the excretion of potassium, and unlike D.C.A. it converted the hypoglycaemic glucose tolerance curves to normal. In one of the patients who had arthralgia of the knees this symptom disappeared during treatment with aldosterone. The new hormone thus seems to combine the effects of deoxycortone with certain properties of cortisone. We now await its synthesis on an economical basis, for if supplies become generally available aldosterone will probably supplant deoxycortone and cortisone in the treatment of adrenal insufficiency.

ENCEPHALITIS IN CHILDHOOD

Twenty-five years ago the term encephalitis was almost synonymous with encephalitis lethargica (von Economo's disease). Since then many other varieties have been described, and encephalitis lethargica is no longer seen. The association of encephalitis with smallpox vaccination caused great concern about twenty years ago, but this complication has become exceedingly rare of late. It is almost never seen when primary vaccination is undertaken in the first year of life. Encephalitis may be due to the direct action of neurotropic viruses and may occur both epidemically and sporadically, or it may be due to poisons or to the toxic or allergenic effects of bacteria. It is known to follow some of the commoner infectious fevers, especially whooping-cough, measles and mumps, and occasionally german measles and chicken-pox, and is one of the very rare, but unpleasant, complications of whooping-cough vaccination. It may also occur in glandular fever and sometimes it accompanies poliomyelitis. Apart from these clear-cut causes there are various infections of unknown aetiology causing encephalomyelitis. The initial diagnosis is usually "influenza" until neurological signs of different kinds appear. Other forms also occur, but are rare. For example, Wernicke's haemorrhagic encephalitis, occurring in infantile beriberi, and the hereditary and familial degenerative diseases such as Schilder's disease have been known for many years. Some authorities would include chorea as a rheumatic encephalitis, citing the not infrequent hemichorea as supporting evidence, but there is scant convincing pathological proof of their association. Dawson[1] has described an encephalitis in childhood which runs a subacute course progressively downwards to dementia and death. The distinguishing feature is the finding of intranuclear eosinophilic inclusion bodies in the neurones, particularly in the cortical grey matter and the basal nuclei. Lead encephalopathy still occurs sporadically, usually in children suffering from pica, and is a serious condition. It should not be forgotten as a possible explanation for convulsions and tremors suddenly afflicting a child known to be given to sucking lead toys or the paint off his cot.

There is as yet no satisfactory classification of encephalitis, though attempts have been made to provide one related to the epidemiology, the aetiology, or the clinical pattern. Children seem to be more prone than adults to encephalitis, and in the last eight years Dr. E. G. Brewis, as he reports at page 1298 of the *Journal* this week, has collected no fewer than 93 cases from the children's wards in three hospitals. Of these 93 cases of encephalitis, nearly one-third followed recognized infections and the rest were of unknown aetiology. No constant relationship was found, either clinically, aetiologically, or pathologically, in the 65 unclassified cases, but Brewis was able to distinguish four main clinical patterns among them. In the first group, consisting of 19 children, of whom 13 were less than 2 years old, the onset was sudden with convulsions and unconsciousness; recovery was rapid or death occurred in a few days. In the second group the disease began with meningeal symptoms, in the third with gradual ataxia and choreiform movements (eight children under 5 years of age), and in the fourth group with somnolence and disorders of the cranial nerves. Despite these fairly typical and clinically different pictures, nearly a quarter of the cases could not be fitted into any one because they overlapped or presented bizarre features.

The comparative frequency of encephalitis in childhood and the mortality (16%), together with the high incidence of severe sequelae in the survivors (19%), combine to make this disease of some importance. There is no effective treatment, but it may present the general practitioner with a problem in diagnosis. In any doubtful case a lumbar puncture should be performed; for this reason, and because of the special nursing that is essential to full recovery,

[1] *Arch. Neurol. Psychiat. (Chicago)*, 1934, 31, 685.

admission to hospital is advisable for all children in whom this diagnosis is likely. While the association of encephalomyelitis with the specific fevers is fairly well known, in the various unclassified forms the diagnosis may be in doubt until the cerebrospinal fluid is examined or neurological signs have become evident. Examination of the cerebrospinal fluid is the key to the diagnosis in most cases. The various forms may present signs and symptoms suggesting meningitis, chorea, cerebral tumour, or an infectious fever with convulsions. The cerebrospinal fluid is usually clear, with a mononuclear pleocytosis and increased protein, but may occasionally be normal, particularly at the outset. The withdrawal of a clear fluid by lumbar puncture excludes meningitis (except tuberculous meningitis and choriolymphocytic meningitis, which have, however, other characteristic findings) and thus is a contraindication to prescribing intensive chemotherapy, which is of no value in encephalitis. The prognosis may be difficult to determine, both of the immediate outcome and of the ultimate mental and physical state after recovery. In general, Brewis found that the mode of onset, the depth of unconsciousness, and the frequency of fits were the immediate guides to the severity of the condition. Viruses, and especially neurotropic viruses, seem to be on the increase. More forms, and more cases, of encephalitis are therefore likely to be seen among infants and children.

INSULIN-RESISTANT DIABETES

Most middle-aged, obese diabetics are strikingly resistant to insulin. The same phenomenon is seen temporarily in severe ketosis, and is a feature of the diabetes associated with acromegaly and Cushing's disease. A.C.T.H. and cortisone may increase insulin requirements if given to patients with diabetes, and Bornstein and Park[1] have recently shown that growth hormone and cortisone in combination are necessary for the development of insulin resistance in diabetic animals. Insulin resistance has also been recorded in patients developing diabetes in association with cerebral tumours affecting the hypothalamus,[2] though no consistent change has been demonstrated in animals with hypothalamic lesions.[3] In the *Journal* this week Dr. J. Beattie reports at page 1287 the production of insulin resistance in rats by interruption of the hypothalamic nerve tracts and removal of the adrenal medulla. Rather surprisingly, neither hypothalamic lesions nor adrenal medullectomy alone caused any upset in carbohydrate metabolism, whereas the combined procedures resulted in hypoglycaemia, with depletion of liver and muscle glycogen and complete unresponsiveness to insulin. Moreover, when glucose was given, with or without insulin, the blood sugar rose to the same extent. The finding that insulin did not lower the blood sugar in these animals is a remarkable one and suggests the presence of one or more insulin antagonists. This has been a popular theory to explain insulin resistance since the experiments of Himsworth and Kerr,[4] and both growth hormone and cortisone may well be insulin antagonists. Evidence from the present experiments suggests that both these substances were present in considerable quantities. Thus adrenal medullectomized animals with hypothalamic lesions put on more weight than the controls, and there was no reason to suppose that there was adrenal cortical insufficiency since normal cortical tissue was found when the animals were sacrificed. Moreover, rats exposed to cool conditions not only increased their oxygen consumption, but managed to regain their pre-operative weight. As the author points out, the interest of these results lies in the possibility that insulin-resistant diabetes may arise from causes which do not primarily involve the pancreas or the pituitary. Nevertheless many problems remain to be solved. Why adrenal medullectomy should result in insulin resistance in the presence of hypothalamic lesions is difficult to understand. It is a well-known clinical observation that patients with Addison's disease are particularly sensitive to insulin, and it is generally thought that the ability to recover from insulin hypoglycaemia is due in part at least to the production of adrenaline. The present study suggests that the presence of insulin antagonists may be more important than the role of adrenaline in the body's response to insulin.

[1] Bornstein, J., and Park, C. R., *J. biol. Chem.*, 1953, **205**, 503.
[2] Paton, A., and Petch, C. P., *British Medical Journal*, 1954, **1**, 855.
[3] Long, C. N. H., *Res. Publ. Ass. nerv. ment. Dis.*, 1940, **20**, 486.
[4] Himsworth, H. P., and Kerr, R. B., *Clin. Sci.*, 1940, **4**, 287.

COLOURED DRIVING-GLASSES

Road travellers returning on Monday night from the Whitsun holiday will experience severe and even dangerous discomfort from the dazzle of on-coming headlights, even though many devices against glare have been put on the market. The dipping of headlights and such-like mechanical measures have done much, but recently some drivers have taken to wearing yellow-tinted glasses in the belief that they absorb selectively that part of a beam of light which produces glare, whether in the more severe form of dazzling or in the lesser form of mere discomfort.

Subjectively such glasses give some drivers the impression that the visual field is brighter, and this has helped to increase their popularity—a popularity spuriously enhanced by the belief that the penetrating yellow light of fog-lamps is useful. There is, however, nothing to be said in favour of yellow-tinted lenses for driving. A clear-glass windscreen transmits 92% of light falling on it, and the lightest yellow filter passes about 88%. A combination of both will pass only 81% under ideal conditions, and considerably less in the presence of dirt and scratches. As might be expected, yellow-tinted driving glasses adversely affect the visual efficiency of drivers, especially at night, when the level of illumina-

tion is low. Richards[1 2] and others have shown that visual acuity falls when using these lenses, and Miles[3] found a reduction not only in visual acuity but also in resolving power and stereoscopic acuity, and, perhaps most striking of all, a slight but definite fall in visual acuity in the presence of glare, itself likely to increase with any scratches on the lenses. Davey and Sheridan[4] have shown that under night-driving conditions the eye is adapted to a much lower level of illumination than is generally assumed, and that the wearing of yellow-tinted lenses is an impediment to detecting faint peripheral stimuli. Yellow-tinted lenses are particularly disadvantageous to colour defectives; Miles[3] has stressed that such people (who are likely to seize upon any device which may help them) have a reduced sensitivity to light, so that even the palest filter will have a marked effect on their night vision. The subjective improvement experienced with yellow lenses may be the result of their sharp cut-off in the blue region of the spectrum. Blue light is scattered more than red, and the eye is myopic for blue light—an effect heightened by "twilight myopia." The beam from a motor-car headlight, however, contains very little blue light.

The use of tinted lenses is not so widespread in Britain as in the U.S.A., where both pink lenses and green windscreens are used, sometimes simultaneously. Green glass is used there to absorb some of the sun's heat which floods through the wide curved sheets of glass at present fashionable in American cars. The fact that some States have banned the use of this green glass is a recognition of its potential danger. There do not appear to be any restrictions on the use of coloured driving-glasses either in Britain or in the U.S.A., but it may be questioned whether the use of coloured screens and coloured driving-glasses do not contravene the requirements of the Road Traffic Act,[5] which lays down that all glass or other transparent material fitted to motor vehicles shall be maintained in such condition that it does not obscure the vision of the driver.

NUMBERING OFF

It might be said of many doctors, especially those who qualified before the last war, that they passed in medicine and failed in mathematics. They are apt to regard statistics with dislike and statisticians with that uneasy respect which King Arthur's knights must have accorded to Merlin. Perhaps this is because statistics often deals harshly with cherished conclusions, as Dr. R. A. J. Asher suggested when opening a debate held last week by the Study Circle on Medical Statistics of the Royal Statistical Society. Proposing that the house should welcome the growing influence of statistics in all branches of medicine, Dr. Asher listed the conventionally accepted applications of statistical analysis in medical research—for example, in assessing the probability that an event occurs by chance; in studying results which might be influenced by several factors; in assessing the significance of apparent correlations, and in revealing those which are not so evident; and in the planning of clinical trials of drugs, when to the clinicians taking part it must sometimes seem that the statistician acts as a kind of *agent provocateur* by including in the trial inert substances indistinguishable in appearance from that under test. But it was in the moral field that Dr. Asher concluded statistics exerted their most beneficial influence. Their salutary discipline could but engender in doctors the twin flowers of modesty and admiration for the works of Nature. Common sense, he said, was not enough, and obvious conclusions could be fallacious.

Mr. R. S. Murley opposed the motion. He found it impossible to disagree entirely with Dr. Asher, but pointed out that the motion referred to *all* branches of medicine. Medicine was an art, statistics a science; he conceded that the latter had its uses, but when it came to mixing science and art statistics was as out of place as a skillet in a Crown Derby tea-service. Doctors and laymen alike read too much into the results of statistical analysis, he thought, which in any case could not give the answer to such human imponderables as the value to the patient of increased survival conferred by a particular line of treatment which left the sufferer a life of chronic invalidism at best or misery at worst.

This aspect of statistical analysis was criticized from the floor by a later speaker, who deprecated the application of statistics to the psychological assessment of personality structure. Another speaker referred darkly to the deliberate misuse of statistics, fostered—for what sinister purpose?—by statisticians themselves. Statistical publications, he said, could be recognized by the prolixity of their tables. In his view no papers should contain any tables at all. The statisticians present coldly ignored this challenge, though the one who framed the motion affirmed that his profession were the champions of common sense, and he urged the house to welcome the growing influence of statistics in all branches not only of medicine but of life itself. Another statistician, supporting the motion, thought that statistical techniques available at any one time might not be of use in medicine, and went on to give a tantalizing glimpse of the technical world of becoming in which statisticians work. Summing up, Dr. Asher said that everyone should be his own statistician, while Mr. Murley struck an undemocratic note in concluding that statistics might be all very well for the elite but were a menace to the mob. On a show of hands the motion was carried by a narrow majority.

The freedom from bias of the opening speakers was emphasized by the revelation that the terms of the motion had been withheld from them until shortly before the meeting. Both had, with an impartiality admirable in two members of a conservative profession, expressed their willingness to speak for or against the motion, whatever it should turn out to be. With such a margin for the operation of chance, the significance of the result of the debate remains obscure. Even if it were not so, can one say, as one speaker did, that significant results are true?

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[1] *Highway Research Board (Washington) Bulletin*, 1952, **56**, 36.
[2] *Highway Research Abstracts*, 1953, **23**, 32.
[3] *Arch. Ophthal. (Chicago)*, 1954, **51**, 15.
[4] *Optician*, 1953, **126**, 33.
[5] *The Motor Vehicles (Construction and Use) Regulations*, 1951, para. 74.

CLINICAL PATHOLOGY IN GENERAL PRACTICE
TESTS OF GASTRIC FUNCTION

BY

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Tests of gastric function have a limited role in clinical medicine. Sometimes simple inspection and analysis of a sample of the gastric contents may contribute towards the diagnosis. A fractional test meal will demonstrate the response of the stomach to various secretagogues, and the varying curves may be associated with different clinical conditions.

Passing of a Stomach Tube

There is considerable individual variation in the ease with which a tube may be passed, but if carefully done a minimum of discomfort is caused. For most patients it is more comfortable to pass the tube through the nose than over the back of the throat. The nose may feel sensitive to the touch of the tube, but this is rarely uncomfortable, and once the tube is down the gullet there is little discomfort in the throat. Pharnyngeal irritation may be uncomfortable when the tube has been swallowed over the back of the tongue and is constantly touching the soft palate. For performing fractional test meals the nasal route is preferable, but if a brief aspiration of the gastric contents is to be undertaken a small but fairly rigid oesophageal tube may be quickly passed through the mouth into the stomach. For performing a fractional test meal, a soft rubber Ryle tube, 42 in. (107 cm.) long, No. 12 French, is probably the most useful one to use. It has a small metal olive at the tip, with four holes between 1 and 5 in. (2.5 and 12.7 cm.) from the olive. Alternatively a Levine tube may be used. This is a round-tipped tube size 14 or 16 F. with four openings in the terminal 3 in. (7.6 cm.). The average distance from the teeth through the cardia is 18 in. (46 cm.), and from the cardia through the pylorus another 11 in. (28 cm.). The nasal route is 2 in. (5 cm.) longer than the oral route.

The tube is well lubricated with water and passed gently into the nostril. As soon as the tube reaches the nasopharynx the patient is encouraged to swallow continuously until the first ring has reached his nostril. He is then allowed a pause and told to breathe through his mouth, while the tube is slid gently down until the tip is well below the pool of gastric juice; in most patients this is about the level of the third ring marked on the tube. Gentle suction is then applied with a syringe. If no gastric contents are obtained, the position is adjusted and a little air is injected. For any research work it is important that the position of the tube should be checked radiologically, but this is seldom necessary in routine clinical studies. It should be appreciated that the tube may curl up in the fundus of the stomach and prevent proper samples being obtained.

Performance of a Gastric-function Test

The purpose of this test should be explained to the patient. He is instructed to have neither food nor drink after 10 p.m. the previous day, the test being carried out early on the following morning. It is best to have the patient sitting upright with his back well supported by a pillow. His nose is inspected to see which nostril is larger, and the tube, well wetted, is then inserted and gently passed as already described. The stomach is emptied and the volume of the residual fluid measured. The free end of the tube is then spigoted and firmly attached to the patient's cheek by strapping.

When the necessary stimulus has been given, samples of about 10 ml. are withdrawn every 30 minutes for two and a half hours. After each aspiration the syringe is washed out with water and a little air is injected down the tube, then the spigot is replaced. One and half hours later gastric juice is tested with Töpfer's reagent, which turns red with acid, or with Congo-red paper, which turns blue if free acid is present. If no free acid is present then an injection of histamine, 0.5 mg., is given subcutaneously. The patient is warned that this will make him feel flushed and may give him a headache, and that there will be redness and irritation at the site of the injection. When the test is completed he is asked to depress his chin on his chest while the tube is withdrawn. Throughout the test he is instructed not to swallow saliva. He should be provided with a receptacle in which to spit. The following are the commonly used tests.

Gruel Test Meal.—This provides evidence of the response of the stomach to a normal food stimulus. Gruel has the advantage of being practically colourless and of such a consistence as not to block the tube. It is prepared by bringing to the boil four tablespoonfuls of breakfast oatmeal with a quart (one litre) of water and then simmering down to a pint (half a litre) and straining through muslin. It is advisable not to add sugar or salt, and on no account must milk be used, as it may effectively neutralize the acid secretion.

Alcohol and Histamine Test Meal.—This is used to demonstrate the presence or absence of achlorhydria. Fifty millilitres of 7% alcohol is given and specimens are taken every fifteen minutes for one hour. Histamine, 0.5 mg., is then given and two further specimens are obtained.

Histamine Test.—By repeated aspiration or by continuous suction it is possible to determine the volume of juice secreted in response to histamine injection; this provides a quantitative estimate of gastric secretory function. With the Ihre technique* a secretion volume at the rate of 180 ml. an hour is taken as indicating hypersecretion. This test is carried out by injecting 0.1 mg. of histamine per 10 kg. body weight and using continuous suction for one hour after the injection. The maximum acid secretory response† may be estimated by injecting four times the normal body-weight dose of histamine. An antihistamine, such as mepyramine hydrogen maleate (100 mg.), should be injected intramuscularly 30 minutes before the histamine is given. This is to protect the patient against the systemic effects of histamine. Continuous suction is applied, and the secretion collected from one-quarter to three-quarters of an hour after the histamine injection is taken as the maximum secretory response. More than 600 mg. of hydrochloric acid an hour suggests hypersecretion.

Indications for Examination of the Gastric Contents

In problem cases with symptoms referable to the upper abdomen—for example, patients with epigastric pain, loss of weight, but with a normal barium meal report—an examination of the gastric contents may help to establish the diagnosis. Examination of fasting juice alone may reveal gross blood-staining from a carcinoma of the fundus, which is easily overlooked radiologically. Gross blood-staining of all specimens in a test meal, together with an offensive smell and a big difference between "free" and total acidity, is strong evidence of a neoplasm, whether or not there is achlorhydria, and a gastroscopy is indicated. If only a blood-staining resting juice is found, it is worth repeating the observation, for a carcinoma of the ampulla of Vater or head of the pancreas can cause bleeding which

Acta med. scand.*, 1947, Suppl. **196, 322.
†Kay, A. W., *British Medical Journal*, 1953, **2**, 77.

can be regurgitated back into the stomach. Again an excessive amount of fasting juice, together with a high-climbing curve, is suggestive of a duodenal ulcer which has been missed radiologically—a further *x*-ray examination is indicated. The odour of the gastric juice must always be noted. The normal pungent odour is lost with a fungating or ulcerating neoplasm, and also with a gastrocolic fistula, and the odour may be very unpleasant.

Another type of problem case is the patient with an anxiety state and abdominal symptoms in whom it is necessary to exclude organic disease. A patient with a physical lesion suffering pain will usually accept a test meal when this is suggested, but a functional dyspeptic commonly reacts vigorously against the suggestion; indeed, the reaction of the patient may be another piece of evidence for or against a physical lesion.

Carcinoma of the Stomach.—It is important to appreciate that a normal acid curve and sometimes a high-climbing curve may be found in patients with carcinoma, particularly in those with small pyloric tumours. At least one-third of the patients with carcinoma ventriculi diagnosed radiologically will have free acid present, but, as mentioned above, there may be a bigger difference than usual between the total and free acid levels. The others will have achlorhydria with a high total acidity but no free acid. If there is a radiological diagnosis of gastric neoplasm but the clinical picture does not fit the diagnosis, it is certainly worth arranging both a test meal and a gastroscopy. Sometimes an unnecessary laparotomy may be avoided.

Gastric Ulcer.—A test meal does not contribute usefully to the management of a patient with a gastric ulcer. If there is any doubt about the benign nature of the ulcer, a gastroscopy is required. Gastric ulcer patients may have high acid curves, but more usually they are normal or low. Absolute achlorhydria does not occur with active gastric ulceration, but it may need additional tests, such as a 24-hourly *p*H test or Kay's special histamine test to demonstrate this (see above).

Duodenal Ulcer.—A test meal is not indicated in the routine management of duodenal ulcer, but may reasonably be done if operation is indicated. A high basal secretion, together with a high level of acidity, may encourage the surgeon to undertake a full 70% resection. Alternatively, a low level of secretion which may sometimes be found may encourage a gastro-enterostomy and vagotomy in a poor-risk subject, and particularly in women, in whom this is still a reasonable surgical procedure.

Chronic Gastritis.—A test meal does not provide conclusive evidence of chronic gastritis, but a low acid curve will be found with an atrophic gastric mucosa. The gastric biopsy technique introduced by Wood and Doig* is a simple method of providing definite histological evidence of the state of the mucosa and gives better information than gastroscopy.

Addisonian Anaemia.—A histamine-fast achlorhydria is a reasonable requirement for clinching the diagnosis, but it is very likely that a "tubeless" test meal will eventually suffice. This depends on the release of quinine by acid from a quinonium resin and measurement of its excretion in the urine.†

Factors Influencing Gastric Secretion

Gastric secretion may be divided conveniently into two phases—the period of digestive secretion and the interdigestive phase. The period of digestive secretion is that in response to meals, and this may be further divided into three phases; the psychic, the gastric, and the intestinal.

The *psychic secretion* is provoked by sight, smell, taste, and even the thought of food, and the secretion evoked is highly acid and rich in pepsin. Vagal section or large doses of atropine will abolish this phase, but it is difficult to measure this secretion in man. In practice, using gruel test meals, this mechanism plays a small and unimportant part.

In the *gastric phase* are three types of stimulating agents which provoke gastric secretory responses. Simple mechanical distension is one mechanism, and it has been shown conclusively that distension of the pyloric part of the stomach stimulates the secretion of hydrochloric acid by the parietal cells of the body and fundus of the stomach. How much of this plays a part in man is still open to question. This secretion can be produced even in a denervated pouch and provides proof of the existence of a hormone for gastric secretion, which is called "gastrin." The second mechanism for acid secretion is the chemical stimulation of the stomach by the products of digestion of food or by food substances themselves. These secretagogues are present in many foods, such as milk, meat, and meat extracts, and in the breakdown products of digestion of proteins. The normal gastric phase of secretion is partly dependent on an intact vagus innervation, and a marked decrease in response to secretory stimulants, such as food, alcohol, and histamine, occurs after a successful vagotomy. It has been suggested that the response of a secretagogue depends upon the basal level of acetylcholine production in the gastric mucosa and thus upon vagal activity. A third mechanism of secretion may depend on actual chemical irritation of the mucosa with liberation of histamine, and this may be the way in which alcohol stimulates gastric secretion.

The *intestinal stimulatory phase* of secretion does not appear to play a significant part in man. More important is the inhibitory effect on secretion and motility that arises from the presence of fat in the intestine, which stimulates the formation of an inhibitory hormone, enterogastrone.

Interpretation of Tests

At one time there was a tendency to relate dyspepsia either to an increased or to a decreased peptic secretion, and a diagnosis of hyperacidity or hypoacidity was regarded as conclusive. Unfortunately this is not so, for both high and low levels of acidity can be found in individuals who are free from digestive disorders. The terminology has been most misleading. Test meals measure a concentration of acidity and not the total output of acid secretion, so that *hyperacidity* is not necessarily synonymous with *hypersecretion.* The concentration of acid in the gastric contents depends on two variables—the amount of acid secreted and the rate of emptying of the stomach. With rapid emptying there may be little fluid left to dilute newly secreted acid, and the concentration may therefore be far higher than if the stomach had emptied more slowly but secreted at the same rate.

At the other end of the scale, the term "achlorhydria" can also be misleading. The limit of free acid is reached when Töpfer's reagent turns from red to yellow. This colour change occurs at *p*H 3.5, which is well above neutrality point at *p*H 7, and there is, in fact, a small amount of free acid left at *p*H 3.5. Normally, however, it is perfectly adequate to take *p*H 3.5 as indicating achlorhydria.

The secretory response to a test meal depends on the quantity and chemical nature of the food, and to a smaller extent on the enjoyment with which it is eaten. The products of digestion of protein, or even their watery extracts, are good stimulants. Starches, on the other hand, are poor secretagogues and their secretory effect is mainly due to distension of the stomach. Nevertheless, the starch test meal has a considerable advantage over a meat-extract meal. The stomach may give an average response to a gruel meal but a hyperresponse to meat extract or alcohol, and the latter would therefore fail to differentiate between a normally secreting stomach and the hypersecretory response associated with a duodenal ulcer. The gruel test meal is commonly used, but the alcohol and caffeine tests are sometimes used instead. Alternatively, the quantitative response to histamine may be measured.

When a gruel test meal is given and samples of gastric juice are taken every 15 minutes, there is an initial fall in acidity followed by a steady increase, with a gradual

Med. J. Aust., 1952, **1**, 593.
†Harkness, J., and Durant, J. A. (1953). *J. clin. Path.*, **6**, 178.

fall after about one and a half to two hours. The initial fall is due to the dilution of the small initial secretion by the bulk of the meal. The increase in acid is often due to the mechanical stimulation of the gruel, which unlike many foods, such as milk, eggs, or meats, does not have any intrinsic secretagoguic action.

Gastric secretion consists of two components: the parietal cell component—that is, hydrochloric acid—and an alkaline secretion from the pyloric glands which, together with mucus, lowers the final level of acidity. The fall in acidity commonly found at the end of a test meal is mainly due to this "non-parietal" secretion; regurgitation of bile and pancreatic juice plays a minor part. The exact mechanism of co-ordination between the acid and alkaline components of the gastric juice is not yet fully understood. There seems to be a normal "brake" mechanism which operates through the duodenum; when the *p*H reaches a certain level an inhibitory mechanism begins to come into action and depresses gastric acidity either by increasing the alkaline component or by decreasing the acid secretion, or both. With duodenal ulcer this "brake" mechanism may be lost, hence the high rising curve sometimes found.

The standard gruel test meal provides a number of points for consideration: first, the amount and appearance of the resting secretion; and, secondly, the shape of the curve, the level of acidity attained, and the approximate rate of emptying of the stomach. The curve is commonly plotted on a printed sheet which gives the limits of the so-called normal responses in a shaded area. It must be remembered that this so-called normal response merely represents the limits which account for 80% of symptom-free subjects. The remaining 20% of normals had either well-marked "hyperchlorhydria" or hypoacidity.

In a standard test meal it is customary to give histamine, 0.5 mg., after one and a half hours if there is no acid present in the stomach by then. Histamine is a powerful stimulus to acid production, but if there is no response to histamine it is still not conclusive evidence of the complete inability of the stomach to secrete acid. For example, in a patient with a histamine-fast achlorhydria and a gastric ulcer, it is possible to get copious free acid for many hours during the day when hourly samples are taken round the clock, yet the histamine response may have been repeatedly negative. The ordinary dose of histamine does not get all the parietal cells into action, and about four times the usual dose is required to do this, but a dose of this size can be given only when covered by an antihistamine drug. This technique does enable one to assess the "total secretory mass" of the gastric mucosa.

Conclusion

The standard test meal is, in practice, full of pitfalls and fallacies, and unless done with care by an interested observer will not justify the discomfort caused to the patient or the time taken in the laboratory. It has been said that the test meal is a much better test of the patient's endurance than of his gastric function. Gagging and retching may cause secretory inhibition and produce an apparent achlorhydria. Achlorhydria, with increased difference between the free and total acid, may be due to the gruel being made with milk or to the patient having had a meal before the test was started. The presence of flecks of blood is sometimes misinterpreted and may be merely due to the trauma of suction on the mucosa. A chemical test for blood is too sensitive and it is better to rely on naked-eye appearance. Appreciable blood-staining is usually significant. The end of the tube may sometimes slip back into the gullet or pass through into the duodenum. Nevertheless, when the test is done by someone with experience and sympathy, particularly if the nasal rather than the oral route is used, it can be made reasonably comfortable and the major difficulties can be avoided.

Next article on Clinical Pathology.—"Laboratory Investigation in the Hyperchromic Anaemias," by Dr. John F. Wilkinson.

A SURVEY OF ST. ALFEGE'S HOSPITAL GERIATRIC UNIT FOR 1952

BY

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This geriatric unit is known as St. Alfege's Hospital II. It is situated in two separate blocks, each of three stories. Each floor consists of one ward divided into two—one for the bedridden, and the other for patients who are up and about. These arrangements have been made for the comfort of the patients and, more especially, to facilitate the work of the staff, particularly at night. The present bed establishment is 268—164 for women and 104 for men. As a considerable number of women patients are under 60 one ward is allotted to them together with diabetic patients. The same need does not arise in the case of male patients, but, on the other hand, there are more surgical and post-surgical cases, mainly due to urinary tract conditions (prostatic hypertrophy, cancer of the prostate, urinary retention, cystostomy), and therefore one ward is allotted to them. Male diabetics have a special ward.

Population Served

The area served by this hospital covers the boroughs of Greenwich and Deptford. According to the latest available figures the population is 170,000 (and therefore the present number of beds represents 1.6 per 1,000). If we regard 14% as being the geriatric group—that is, persons of pensionable age—this would amount to approximately 24,000, and therefore there are available 1.1 beds per 100 for the group.

It is well known that the social structure of the population is of great importance when assessing the number of beds required for elderly people. For instance, it is likely that a hospital situated in an upper-class residential area might require fewer beds than one in a working-class district. The population in our area consists almost entirely of weekly wage earners; most members of the family go out to work, and neighbourly help is therefore seldom readily available. Housing conditions are sometimes poor, with overcrowding. As a result of these circumstances there is often a heavy demand for hospital beds for old people. A large proportion of the population, mostly women, live alone, and the additional burdens which accompany winter may well bring their slender resources, already stretched to the utmost, to breaking-point, and compel them to seek hospital admission.

Admissions

During the year under review 300 women and 246 men were admitted. Requests for admission come from the following sources: General practitioners, acute wards of St. Alfege's and Mjller Hospitals, the Emergency Bed Service, the medical officer of health, receiving-room, and other hospitals (teaching, cancer hospitals, etc.).

The procedure for the admission of patients put on the waiting-list by general practitioners is as follows.

In the late spring and through the summer, when the number of applications is not large, patients are admitted solely on their doctors' recommendations, because it is thought that even those patients who need residential rather than hospital accommodation will benefit from a stay in hospital before moving on to a local authority home.

Patients who are mentally deranged often benefit in the same way, but if after a period of observation their mental condition does not improve the advice of the consultant psychiatrist is sought. On his recommendation suitable patients can be transferred to Tooting Bec Mental Hospital,

where those over 70 are received for observation and treatment without being certified. Only occasionally do we find any reluctance on the part of the family to such an arrangement; when there is any reluctance it can usually be overcome by explaining the position. In very rare circumstances does a patient have to be certified, and, in fact, this was necessary only once during the year.

During the autumn and winter, when there is a heavy demand for hospital beds, the procedure for admission is different. Each patient who is put on the waiting-list by a general practitioner is visited and examined at home in order to assess his priority, which is based roughly on these grounds: (*a*) recent cerebrovascular accidents; (*b*) medical cases which should respond to treatment and be made fit for discharge in a short time; (*c*) medical cases which will require a longer time to be made fit for discharge; (*d*) patients requiring admission on social grounds not referred by the medical officer of health (the medical officer of health's patients have priority); (*e*) mentally deranged patients who may be put on the waiting-list for Tooting Bec Hospital; and (*f*) mental patients who cannot be kept or certified at home.

Stay in Hospital

After admission to hospital patients receive the necessary medical treatment, including physiotherapy and occupational therapy, both remedial and diversional. During their stay the lady almoner greatly assists by relieving their worries and, when necessary, putting their home affairs in order. Later, when the time for discharge has come, she supplies information on whether the home conditions are suitable for the patient's return. She may arrange for the district nurse to call or a home help to be supplied, or for such other assistance as is given by the Red Cross, St. John Ambulance Brigade, Women's Voluntary Service, Old People's Welfare Committee, and so on. Should the patient not have a suitable home, application is made to the local authority for accommodation. These transfers are arranged smoothly on an exchange basis, thus enabling patients in Part III homes to receive hospital treatment.

A high percentage of elderly people are mentally deranged as a result of arteriosclerotic processes of the brain, chronic softening of the brain, and so on. Such patients will be considered for transfer to Tooting Bec Hospital.

We have noticed a striking increase in the number of readmissions, and we regard this as a welcome and salutary phenomenon. As in the case of younger rheumatic heart patients who spend their lives between periods of some activity and periods for repair in hospital, it is a good policy to give old people periods of treatment and rest prophylactically, and thus prevent or delay deterioration where further recovery is not possible.

Discharges

Discharges for the year under review numbered 321. Seventy-two patients (23%) were transferred to local authority homes and Tooting Bec Hospital, or, if in need of specialized treatment such as neurosurgery, to other hospitals. The other 249 (77%) discharged patients returned to their own homes: this does great credit to the patients' relatives, who showed themselves willing to accept the task of caring for an invalid, often infirm and frail.

On discharge the patient is told to inform his doctor that he is at home again. By this time the general practitioner has received a summary of his patient's diagnosis, treatment, and other pathological and radiographical information. The patient is also visited by a health visitor from the London County Council Health Department, who sends a report to the lady almoner for the information of the doctor in whose charge the patient has been during his stay in hospital.

Patients are seen and followed up in a geriatric outpatient clinic and, when necessary, readmitted or provided with further amenities at home.

Long-stay Cases

The problem of long-stay hospital patients is one of great importance, for these reduce the turnover in hospital beds. The recognition of the factors which necessitate a long period in hospital may help to solve the problem. Those who remain in hospital longer than a year fall into three main groups:

(1) *Chronic Joint Conditions.*—There were 64 cases: 11 had rheumatoid arthritis; one had Charcot's syphilitic osteoarthropathy of hip-, knee-, and ankle-joints; and 52 had osteoarthritis of different localization, but chiefly of hip- and knee-joints. It is easy to fall into controversy on the problem of osteoarthritis in elderly patients. It is well known that all people over 60 have osteoarthritis, but not all are sufferers. The condition may be more or less marked or more or less dispersed. The discomfort and apperception vary from nil to 100%. Very many patients with thickened phalanges suffer psychologically without sustaining pain or impairment of movement. On the other hand, some patients are completely crippled by osteoarthritis of the hips. To suggest that osteoarthritis in these patients is the primary cause of admission to a geriatric hospital or of incapacitation would be incorrect. Many patients are admitted for other reasons, such as cerebrovascular or cardiovascular diseases, and even a marked osteoarthritis may be an accidental finding. There are, of course, many patients who seek admission only on account of osteoarthritis, particularly of the hip-joints. Their history often reveals that for months or even years their treatment has consisted in resting in bed, which frequently results in severe contractures. The 11 patients with burnt-out rheumatoid arthritis, in addition to being over a year in this hospital, spent several years in other hospitals during the active stage. The problem of rheumatoid arthritis in active and non-active stages is beyond discussion here.

(2) *Disseminated Sclerosis and Other Nervous Disorders.*—One man and five women suffered from this disease; three of the women were paraplegic.

(3) *Arteriosclerosis.*—Patients suffering from this illness form the bulk of long-stay cases, and they are discussed below.

Deaths

During the year 238 patients (124 men and 114 women) died. There were 12 coroner's post-mortem cases, 9 of which were held because death occurred within 24 hours of admission, two on account of fractures sustained at home before admission, and one sustained in the ward. Fifty patients died of cancer (34 men and 16 women), the distribution being as follows:

Men

Alimentary tract (pharynx 1, stomach 9, pancreas 1, rectum 6, colon (ascending) 1)	18
Urinary tract (bladder 1, prostate 5)	6
Lung	9
Sarcoma of muscle (patient aged 54)	1

Women

Alimentary tract (stomach 1, liver 2 (primary), gall-bladder 1, colon (ascending and transverse) 3, rectum 1)	8
Metastases in abdomen (primary not found)	1
Urinary tract (bladder 1, uterus 2—1 corpus, 1 cervix)	3
Breast	2
Lung	1
Cerebellar tumour	1

The causes of death in the remaining cases were chiefly of cardiovascular origin—primary, or secondary to chronic pulmonary disease such as emphysema and chronic bronchitis with chronic pulmonary heart.

Deaths during the year were as follows: January to March, 52; April to June, 44; July to September, 58; October to December, 84. The increased number during the last period can be largely attributed to the fog.

Conclusions

It is evident that an allocation of 1.1 beds per 100 of the geriatric population should be enough under normal circumstances, and only in the event of an exceptionally severe winter or epidemics of serious upper respiratory infections might a temporary shortage of beds arise. To

ensure that a high rate of turnover is maintained it is essential that such patients as those suffering from osteoarthritis should be treated in the early stages and encouraged by persuasion and physiotherapy to be mobile. Further improvement in the position could be effected by the development of clinics for rheumatic out-patients. These, if the patients were encouraged to attend conscientiously at the onset of illness, would prevent or delay immobility, thereby easing one of the burdens on the geriatric hospital.

The bulk of long-stay cases are those suffering from arteriosclerosis, especially of the brain, with consequent inability to walk, incontinence, and mental deterioration. Such patients need special accommodation, as they require little more than nursing supervision. We are convinced that it is of the utmost importance to create intermediate accommodation between Part I (hospital) and Part III (local authority), which should offer to suitable patients the attention and nursing which they require.

These "nursing annexes" would accommodate bedfast patients incapacitated through cerebrovascular accidents; disseminated sclerotics if they are paraplegic; incontinents; burnt-out rheumatoid arthritics; and those beyond the reach of active medical treatment, such as persons immobilized through severe osteoarthritis and advanced arterio-cerebral sclerosis. These "nursing annexes" would require only a small trained nursing staff, as the patients' chief needs—care and attention—could be provided by orderlies working under trained supervision. Medical supervision would be in the hands of the geriatrician, and such day-to-day care as was necessary could be given by the house-physician of the geriatric unit.

I should like to express my appreciation of the co-operation extended by the general practitioners in Greenwich and Deptford, who are carefully selecting their patients for admission, thus enabling us to admit really needy patients with little or no waiting.

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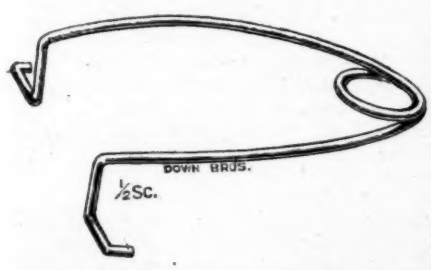
Preparations and Appliances

SIMPLE THYROID RETRACTORS

Sir HENEAGE OGILVIE writes: In 1953 the surgeons of Wellington, New Zealand, gave me the privilege of taking part in a three-weeks postgraduate course in surgery as a member of the staff of the Wellington Hospital. I was allowed the use of 25 beds, allotted a very able house-surgeon and ward sister, and given two operating days a week.



For a thyroidectomy I was provided with a pair of retractors of a type new to me, and better than anything I had seen in England. I was unable in the time to buy some for myself, but on my return I drew what I wanted and asked Down Bros. to make them for me. The idea comes from the Wellington Hospital, but I cannot say who designed them, nor can I claim that mine are a true copy of the originals.

As will be seen from the figure, the retractors might be described as a pair of large opened hairpins made of spring wire, with the points bent down. After the skin flaps have been turned up and down, towels are laid over them, and a retractor, closed by compression, is put under the edge of the towel and skin on each side of the midline and allowed to spring open. The points of the retractors should be about an inch (2.5 cm.) apart above and about 2 inches (5 cm.) apart below. Towel forceps are used to clip the towels at the ends of the incision, and as they drop back they hold the elbows of the retractors back as well. These retractors give adequate exposure, stay in all the time, are never in the way, damage nothing, are cheap, and need no repairs. *O si sic omnia.*

Nova et Vetera

SWEDISH PIONEERS OF MEDICINE GO TRAVELLING

In a "Docent" lecture published in the organ of the Swedish Medical Association, *Svenska Läkartidningen*, for September 4, 1953, Dr. Wolfram Kock, of Stockholm, shows how, in the past, if you wished to end up as a pioneer of medicine you had to travel far and see much in your youth. Not a bad thesis even now. His material consists of two distinguished quartets. The first was composed of Olaus Rudbeck, Petrus Hoffvenius, Urban Hiärne, and Johan von Hoorn, who made their mark in the seventeenth century.

A Seventeenth-century Quartet

Olaus Rudbeck was the discoverer in 1650 of the thoracic duct—a discovery made independently of the Frenchman Jean Pecquets, whose identification of this duct dates back three years to 1647. In 1652 Rudbeck's discovery of the lymphatic glands and lymphatic system earned him renown and an invitation to demonstrate this system to Queen Kristina of Sweden. When he finally settled in Sweden he founded the botanical garden in Upsala, having taken seeds and plants from Holland wherewith to stock it.

Hoffvenius, who died in 1682, had already successfully defended two theses, entitled respectively "De Oculo" and "De Symptomatibus," when he set off in 1658 for Leyden on a royal scholarship. After studying anatomy there he returned to Sweden in 1661, and was appointed professor of medicine "et Physices" in Upsala. His gifts as a physician earned him the title of the "father of Swedish medicine," but for want of hospital accommodation he taught his students by taking them with him on his rounds to his patients—a system he had learnt in Leyden.

Hiärne was only 25 years old when he set out on his travels as personal physician to a high Swedish official appointed Governor of Riga. From there he travelled to Germany, Holland, England, and France, and he spent three years studying chemistry in Paris under Christopher Glaser, apothecary to Louis XIV. On his way home from Paris in 1673, Hiärne picked up a useful tip from the famous Dutch doctor Helvetius, who told him that ipecacuanha was a cure for dysentery. The Polish campaign by Charles XII of Sweden was at this time seriously complicated by dysentery, for which the new drug proved a godsend under Hiärne. As well as being a popular physician in Stockholm, he was instrumental in founding Collegium Medicum, an organization for the control of the practice of medicine in Sweden.

Johan von Hoorn, the "father of Swedish obstetrics," earned this title by his prolonged studies in Leyden and Paris. By September, 1687, when he reached Paris, he had already mastered the literature of his subject, but still felt in need of some practical experience. He would have liked to acquire it at the old hospital, Hôtel Dieu, where a whole ward was set aside for obstetrics. But foreigners were not welcome here at this time, so Hoorn had to learn his trade by joining forces with a Madame Allegrain, known

to be a "wise and very quick" midwife. She had a large practice among the poor of Paris, and by tipping her patients judiciously Hoorn was allowed to be present at their confinements. There was only one snag: Madame Allegrain was not allowed to operate. So Hoorn got into contact with a Monsieur Le Frad, a duly accredited "accoucheur" who had mastered the technique, for what it was worth at that time, of the treatment of "partus praeternaturalis." Obstetric forceps had been discovered by this time, but were a strictly guarded and secret monopoly into whose cult Hoorn was never admitted. On his return to Sweden he took an active part in converting the "unscrupulous drunkards" practising as midwives at that time into a semblance of well-trained midwives.

An Eighteenth-century Quartet

The next quartet of Swedish pioneers of medicine was composed of Nils von Rosenstein, the botanist Carolus Linnaeus (raised to the nobility with the title of von Linné), Abraham Bäck, and Olof Acrel, the "father of Swedish surgery."

Rosenstein is perhaps best known to the vulgar world of to-day on account of his chest drops (vinum glycyrrhizae opiatum), still an infallible remedy. The son of a clergyman, Rosenstein was originally destined for the Church, and he had already pursued theological studies when he switched to medicine. In order to become a university teacher he studied abroad, first at Halle and later at Turin, Montpellier, and Paris. At the small university town of Harderwijk he graduated in medicine in 1730 with a thesis entitled "De Historiis Morborum Conscribendis," which in plain terms means the art of keeping case records. In 1740 he was appointed professor of natural history, with the task of teaching anatomy, physiology, pathology, and practical medicine. He also became the author of the first Swedish textbook of anatomy.

Linnaeus is so famous as a botanist and zoologist that his possession of a medical degree is often overlooked. His travels abroad between 1735 and 1738 brought him to Denmark, Germany, Holland, England, and France. At Harderwijk he graduated as doctor of medicine on a thesis written in Swedish and entitled "Hypothesis Nova de Febrium Intermittentium Causa." Here he showed that the clay content of drinking-water was the cause of intermittent fever or ague. He is said to have defended this thesis with "presence of mind and great ingenuity." At Leyden Linnaeus was anxious to meet the intellectual giant of his day, Boerhaave, old and rich and much sought after by his patients. To get Boerhaave's ear you had to tip his servants properly, and it took the penniless Linnaeus a week to secure an audience, for which he had applied in writing. But in due course he and Boerhaave became the best of friends, and the grateful Swede called his Dutch teacher "my father in medicine." Clinical medicine as well as botany was discussed by the two, and in 1737 Boerhaave suggested to Linnaeus that he should take part in a botanical expedition to Dutch Guiana. As a bait for this undertaking, Linnaeus was informed that a predecessor holding the same appointment for five years had secured some barrels of gold in a salubrious climate producing beautiful plants. But Linnaeus seems to have been more impressed by Boerhaave as a scientist than as a promoter of gilt-edged expeditions to the Tropics.

Abraham Bäck was disappointed in his youth over some academic appointment, so he undertook foreign studies wherewith to equip himself for later promotion. Setting forth in 1741, he spent four years abroad, studying anatomy and botany in Leyden. Later he proceeded to England, where, with introductions from Linnaeus, he visited Oxford, the botanical gardens in Chelsea, and the naval hospital at Greenwich. Going to Paris in December, 1742, Bäck spent two years studying anatomy, surgery, pathological anatomy, internal medicine, botany, and zoology. He learnt how to make anatomical preparations by injections and other methods, and he studied pharmaceutical chemistry at the Jardin des Plantes. He was also diligent in going the rounds of the Hôtel Dieu. On his return to Stockholm in 1745 he became a teacher of anatomy and soon afterwards Court physician. He took an active part in founding a hospital for the combined care of the sick and the training of physicians. With his Paris background, Bäck was naturally inclined to think in terms of the Hôtel Dieu. But he was shrewd enough not to swallow Hôtel Dieu standards wholesale, with each bed shared by two or three bedfellows and in the maternity ward by four bed-fellows at a time. For in Bäck's plan for a new hospital in Stockholm he referred specifically to "hospital wards with beds in two rows and only one person in each bed." One of his arguments in favour of a hospital for Stockholm was that "a well-equipped hospital should also render costly studies abroad superfluous." When the Serafimer Hospital was opened Bäck became as a matter of course its first medical superintendent.

Olof Acrel, also one of the founders of the Serafimer Hospital, learnt much of his surgery abroad under stormy conditions. Travelling through Denmark to Germany, he studied anatomy and physiology under Albrecht von Haller and surgery under Richter. However, he soon moved on, as there were only four corpses for dissection each year. In London he studied operations for stone under William Cheselden at St. Thomas's Hospital. War having broken out on the Continent, Acrel fitted himself out with surgical instruments at Strasbourg and joined the French Army as a surgeon. In the autumn and winter of 1743–4 he was a senior surgeon in the fortress of Lauterburg, where he had some 1,200 patients and 24 assistant surgeons under his care. When the fortress was taken in 1744, Acrel became a prisoner of war, but he was allowed to return to Sweden in the autumn of the same year. On the initiative of the Swedish Academy of Sciences, he published a study of hospital administration in connexion with the new Serafimer Hospital, to which he was attached as senior surgeon for 54 years, with the title of professor and general director.

CLAUDE LILLINGSTON.

Opening a hostel for rheumatic sufferers at Bracken Hill House, Northwood, Middlesex, last week, Miss PAT HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, referred to the "unremitting research" that is going on. Since the war, she said, the financial support given to research on rheumatism both by voluntary and by governmental agencies had substantially increased. Research centres up and down the country now received steadily increasing support from the Medical Research Council, from the regional hospital boards, from many university departments of medicine, as well as from voluntary organizations such as the Nuffield Foundation. The Ministry would watch with great interest the present venture at Bracken Hill House, the fundamental idea of which was to enable patients to be temporarily resident near a hospital which possessed specially experienced medical staff as well as adequate treatment facilities. The British Rheumatic Association rightly regarded this as a pioneer effort, and it was, of course, a field of experiment for which voluntary effort was pre-eminently suited. Such pioneer ventures were always difficult for a Ministry to promote, but experiments by voluntary organizations often provided a useful guide to later official action. She welcomed the financial support which industry had given ventures such as this, for to them rheumatism presented a grave manpower and production problem. She said she was also glad to know that a two-years financial guarantee had most generously been given by LORD NUFFIELD of £1,000 a year against loss in operation. It was of particular interest that patients for the 25 beds with which the hostel was starting would initially be mainly drawn and selected from industry. The interests of the British Rheumatic Association were, of course, national in scope, and she understood that the association was exploring the possibility of similar hostels in other areas. She said the Ministry welcomed such experiments and would watch keenly and be ready to learn from the results.

FACIAL PARALYSIS

The first of what is hoped will become a series of informal discussions on clinical problems was held by the Ciba Foundation on May 10, the subject being the treatment of facial palsy. Dr. BASIL KIERNANDER was in the chair.

Miss JOSEPHINE COLLIER spoke first and stressed that it was important to differentiate between the pre-degenerative phase of the nerve lesion and the phase of established degeneration. Treatment should begin in the pre-degenerative stage and should be designed to prevent actual degeneration. Mr. TERENCE CAWTHORNE said he performed decompression two to three months after the onset of symptoms if there was still no voluntary or faradic response. One-third of these cases showed signs of recovery one week later. He believed local ischaemia to be an important factor in these cases. Wing-Commander P. F. KING gave the results of 160 cases treated in the R.A.F. Of these, three-quarters were Bell's palsy. The treatment was stimulation of the facial muscles by interrupted galvanism until voluntary mobility returned; thereafter active exercises were practised in front of a mirror. Fifty-eight per cent. of his cases had some form of splint. The rate of recovery was as follows: by two months 56% had recovered, by three months 70%, by six months 84%, by twelve months 90%, and over one year 94%. Of these, a total of three had to have fascial slings.

Dr. RITCHIE RUSSELL said the peripheral nerve lesions behaved as pressure palsies which either recovered rapidly or showed degeneration. A nerve could conduct impulses for 24 hours without a blood supply, and he suggested that the logical times for decompression would be in the first few hours of symptoms, or as soon as the reaction of degeneration occurred, or at eight or nine months. The treatment of paralysed muscles should not consist in keeping them permanently relaxed, and they should be put through a full range of movements daily. Mechanical support was necessary only with sagging. Dr. A. T. RICHARDSON said that the main points to decide were whether there was a nerve block or whether degeneration had occurred. He stressed the importance of testing for nerve conduction, stimulating the facial nerve as it emerged from the stylomastoid foramen. If nerve conduction was present at the fifth day there was a fair prognosis, if at the seventh day a good prognosis, and at the twenty-first day a very good prognosis, for no further degeneration usually occurred after twenty-one days. For treatment he agreed that short-wave diathermy or anodal galvanism applied to the stylomastoid foramen were of no value, and he used interrupted galvanism as previously described. Mr. D. N. MATTHEWS described his operation of fascial sling where the mouth was motored by the masseter muscle and the eye by the temporalis. Mr. C. R. MCLAUGHLIN said there were three ways in which plastic surgery could help. The first was static support of the corner of the mouth and cheek; the second was reanimation with rounding of the cheek and corner of the mouth; and the third was the relief of epiphora. His indications for operation were complete failure to recover or partial recovery after five years.

The meeting closed with a vote of thanks to Dr. Wolstenholme and the Ciba Foundation.

A convention on social insurance, dealing with benefit for old age, widowhood, orphanhood, and industrial injuries, has been signed with Switzerland. It provides, among other things, that a national of either country who has qualified for benefit in one of the two countries shall receive that benefit while he is resident in the other country. It also relaxes the nationality conditions of the Swiss scheme in favour of citizens of the United Kingdom and Colonies; insured persons who have not paid enough contributions in one country to qualify for a pension under that country's scheme are enabled to receive a supplement to the pension payable by the other country. Any person in Great Britain who may be affected by the convention should get in touch with his local Pensions and National Insurance Office.

Correspondence

Undergraduate Education

SIR,—The Report of the Undergraduate Education Committee of the Council of the College of General Practitioners (*Journal*, May 15, p. 1146) emphasizes what have been the opinions of many of us for years, and adds some useful new recommendations in the form of answers to a questionary, rather than as a statement of the opinion of the Committee and Council based upon a summation of the individual opinions of general practitioners represented on the fifteen regional faculty boards.

It is indeed good to read that the great majority of doctors urge that the boy and girl while still at school should continue to receive a "broad general education" in the humanities before bending his or her entire thought to specialize in the materialism of the natural sciences. It is amazing that some universities should have so far forgotten their true function by insisting that the first premedical examination should be passed before leaving school.

The Report also repeats the criticisms, which have been voiced for years, of the undue time wasted in learning the unessential minutiae of anatomy, and those of more recent date, of the professorial type of teaching of medicine. For the student medicine now is little more than biochemistry, physical mechanical methods, and a mass of various diagnostic tests. Here is an illustration. Some three years ago, while walking through a maternity ward with a group of students, I stopped before a pregnant woman propped up in bed with glaring exophthalmos and a large lump in her neck. I asked one young man—who had "done his medicine"—"What is her trouble?" He looked at her for half a minute and then said, "I should first like to know her blood-cholesterol." Perhaps a knowledge of her blood-rhubarb would have been equally helpful in making a diagnosis!

The Report also stresses the necessity for instruction in the common disorders of daily general practice. Again, this has been urged on the schools for years, but still the teaching is deficient. How often does the student hear a talk on the man who tells us that he feels "run down," or the other who complains of increasing fatigue? I am surprised, however, to find no specific mention of the importance of teaching of so-called functional disease or symptoms without discoverable physical signs. This is a group of disorders which comprise, perhaps, three-quarters of all the patients we see, primarily based nearly if not always on disturbances of the mind and emotions. Psychiatry is mentioned along with three or four other incompletely taught subjects, but psychiatric patients are apart from those suffering from the many neuroses which belong to all the branches of medicine.

That no reference is made to the teaching of psychology, "the motives and mechanisms of the mind," as expounded some years ago by Graham Howe, is a reflection on the choice of questions submitted to the faculties and on those who answered the questionary, inasmuch as they neglected one of the most important of all the omissions in clinical teaching. By all means let the student be taught more about the common things—"run down," fatigue, insomnia, obesity, food, loss of weight, leucorrhoea, swollen ankles, "wind," constipation, and many others—but also give him much more emphasis on the protean manifestations of neurosis and functional disorders.

I wrote to you, Sir, in December, 1932,[1] on the urgent necessity for including some teaching on psychology in the curriculum, but even in 22 years there has been so little progress that still the student regards the neuroses as "clinical rubbish" to be passed from one out-patient department to another.—I am, etc.,

London, W.1. ALECK BOURNE.

REFERENCE

1 *British Medical Journal*, 1932, 2, 1122.

Women in Medicine

SIR,—There has been lately some discussion (*Journal*, May 15, p. 1143) of the marriage of medical women. I do not consider that the essential problem has yet been mentioned—that until a woman is a satisfied mother she is not a complete personality and cannot perform to the full her functions as a doctor or anything else. I base this opinion on observations of myself and of my friends and acquaintances, medical and otherwise. Further, once a woman has babies her first duty is to them and she can only give second place to a career. It follows that until her family is off her hands no woman can take a man's part in a profession.

I see in this no reason why women should not train for medicine, do useful medical work in their child-bearing years, and proceed further in their careers at middle age. Surely it is wrong that women of high intellectual powers and good education should be discouraged from early marriage and a large family on the grounds that their education will be wasted. They usually marry men with intelligence equal to or higher than their own. Their own single contribution to the common good is unlikely to equal that of their children, even if they devote all their energies to their career.

I had to choose between marriage and taking a higher degree and all that it would lead to. I married, and now have three small sons. I have never been out of full-time medical work; although since I started the family this has been in the humble, but very useful, position of school medical officer and medical officer at a maternity and child welfare clinic (in this job, incidentally, I find my personal experience at least of as much value as my medical training).

Surely young women going into medicine should be encouraged to marry and make full use of their experience both as doctors and as well-balanced women, not to put all their energies into their careers.—I am, etc.,

Wednesbury, Staffs. HAZEL B. BAKER.

Early Recurrent Acute Intussusception in Children

SIR,—The article on recurrent acute intussusception (*Journal*, March 6, p. 559) prompts me to report a recent case.

A baby girl, aged 1 year, was admitted on August 9, 1953, with a history of blood in the stools and diarrhoea for the past two days. Increased bowel sounds were present and palpation of the abdomen showed a soft tumour in the left hypochondrium. At laparotomy an ileo-colic intussusception was found. This was reduced easily, and post-operative convalescence was uneventful.

The child was brought back from a distant village and re-admitted on November 26, 1953, with a history of recurrent attacks of vomiting, constipation, and abdominal distension on taking food. On examination of the abdomen no tumour could be felt, but ingestion of half a cup of water produced a typical ladder pattern. Laparotomy disclosed an ileo-colic stricture adherent to the left costal region; the caecum, appendix, and colon up to the splenic flexure could not be demonstrated. A resection of the stricture and two inches (5 cm.) of bowel on either side was performed with primary anastomosis. Post-operative convalescence was satisfactory and the child is now quite well. Examination of the specimen showed a stricture present the calibre of which did not exceed 5 mm. at its narrowest point. Apparently recurrence of the intussusception had occurred with sloughing of the intussusceptum, leaving a fibrous stricture.

I have to thank the Director of Medical Services, Sudan Government, for permission to report this case.—I am, etc.,

Juba, A.E. Sudan. H. H. BARST.

SIR,—Following on the article by Mr. David A. Macfarlane and Mr. L. P. Thomas (*Journal*, March 6, p. 559) and the letter by Dr. Erik Christensen (*Journal*, May 15, p. 1151), it might be of interest to record yet another case of this somewhat rare condition.

An English female baby 4 months old was seen by me in Mbeya, a town in Tanganyika Territory of East Africa. The mother gave the history that the child had been fretful and had what appeared to be abdominal colic. No faeces had been passed for 24 hours, but napkins had been soiled with some blood-stained mucus. On examination I found the child to be restless and tearful, but otherwise in good condition. It was not possible to palpate a tumour, the abdomen being resistant to touch. Owing to the primitive facilities available to confirm the diagnosis, the rather serious decision to operate had to be made on the history, which contrasted with the previous normal habits of the child and which, in conjunction with the blood-stained discharge, indicated some pathological obstruction in the abdomen and suggested an intussusception. A saline irrigation of the lower bowel failed to produce any result either in the production of faeces or in the reduction of the obstruction. After sedation a midline laparotomy was performed under heavy cinchocaine spinal analgesia. This was administered through an 18 gauge hypodermic needle. On opening the abdomen an ileo-colic intussusception about 2½ in. (7.5 cm.) long was found; this was reduced and the abdomen closed. Three weeks later the same picture recurred. A further operation was performed again under spinal analgesia. On this occasion after reduction of the intussusception the appendix was removed and the stump fixed by a stitch to the lateral wall of the abdomen. The use of spinal analgesia in this case was necessitated by the lack of a trained anaesthetist.

The child is now 6 years old and is well, having had no recurrence of this condition.—I am, etc.,

Epping, Essex. J. F. LUCEY.

The Children's Nutrition Council

SIR,—May I briefly record the fact that the Children's Nutrition Council, the organization originally established by Miss Eleanor Rathbone, Sir Gowland Hopkins, and others in 1933, has now decided to terminate its existence? Many of your readers may remember that the Council (first called the Children's Minimum Council) campaigned for a number of years to promote legislation on the various nutrition services. During the war its members interested themselves in the developing of school meals and in the growth of the various milk and vitamin schemes. With the close of the war it became evident that the aims of the Council had all been achieved, even if much still remains to be done to improve the administration of the services themselves. Some doubt was felt whether in its existing form the Council had any further work it could usefully do; and with the deaths of several of its leading members the time seemed to have come to wind up its affairs. A small balance in hand has by committee resolution been transferred to the National Society of Children's Nurseries on the understanding that it is to be used to assist research and publications on the care and feeding of young children.—I am, etc.,

London, E.C.1. F. LE GROS CLARK.

Treatment of Threadworm Infestation

SIR,—Our lack of knowledge concerning the intestinal conditions favourable to threadworm infection, which Dr. Gwyneth M. Cotterell laments (*Journal*, May 8, p. 1099), is partly due to the fact that the *Enterobius vermicularis* cannot by any known means be kept alive *in vitro*. It is, nevertheless, difficult to accept Paterson's view[1] that debilitated children "fail to digest and kill off the swallowed ova" owing to low gastric HCl output, for threadworms commonly infect perfectly healthy children. The numerous surveys undertaken indicate that the incidence of enterobiasis in children is well above 50%. In adults it is generally lower; for instance, it is as low as 2% in Chinese students, yet as high as 72% in inmates of a mental institution[2] and 64% in patients incapable of attending to personal hygiene.[4] These findings suggest that simple hygiene is probably the main factor which determines perpetuation of infection, while variations in the intestinal environment may have no influence at all. I would welcome other views on this matter.

I am not convinced that any symptoms other than pruritus and its sequelae can be ascribed to enterobiasis. The majority of children harbouring the worms have, in fact, no symptoms at all. One reads that threadworms cause

appendicitis, but it is hardly surprising that two common conditions should occasionally coincide.

Since the introduction of piperazine hydrate[5] the treatment of enterobiasis has been greatly simplified and it is no longer "more troublesome than the worms themselves." In my experience with this drug enemas, suppositories, purging, and starvation have no place whatever, and very few side-effects have been observed. It should not be necessary to treat *symptomless* enterobiasis; but it is worth while remembering that the commonest cause of failure in obstinate cases is undoubtedly the presence of a symptomless "carrier" in the family, who is responsible for reinfection. Detection of ova, using the adhesive "sellotape" technique, should present no difficulty.—I am, etc.,

Bristol. R. H. R. WHITE.

REFERENCES

1 *Sick Children*, 1938, p. 517. London.
2 Kao, C. M., and Chow, Y. L. (1951). *Peking Nat. Hist. Bull.*, 19, 267.
3 Petersen, M. C., and Fahey, J. (1945). *J. Lab. clin. Med.*, 30, 259.
4 Heilmann, C. G. (1950). *Amer. J. trop. Med.*, 30, 93.
5 White, R. H. R., and Standen, O. D. (1953). *British Medical Journal*, 2, 755.

Clergy and Doctors

SIR,—There have been in recent years experiments on this question of co-operation between clergy and doctors. The National Council for Pastoral and Medical Co-operation was founded in 1938 with an ambitious programme, and at least six groups of clergy and doctors were formed in the larger centres. But it was found impossible to continue activities throughout the war years, and the council was dissolved in 1942.

One important fact did emerge. Effective co-operation can only be satisfactorily initiated and maintained on a personal basis. It is little good expecting that clergy and doctors, just because they happen to live in the same locality, can necessarily join together in their dealings with the sick. It is only when a relationship of mutual confidence has been established between individuals of the two professions that the project can hope to work.—I am, etc.,

London, W.1. H. C. SQUIRES.

SIR,—The letters of the Rev. Tony Clemens (*Journal*, April 24, p. 983) and Dr. F. Gray (*Journal*, May 1, p. 1041) are interesting as showing the trend of the times—the upward thrust of the spiritual in the medical as in many other walks of life. I think that there are many points of contact between the orthodox Christian clergy and the medical profession, both individual and collective; but I should like to name a few fairly well known groups or societies interested in the welfare of "the whole man."

There is a St. Luke's Society with headquarters in London and a priest-doctor as secretary. There is a Christian Medical Fellowship sited in Liverpool to which many eminent members of the profession belong and which holds conferences offering "unique opportunities for quietly considering and reaffirming those Christian values so many feel to be basic to the practice of medicine." There is the Guild of Health, a flourishing society with headquarters at the Edward Wilson House, 26, Queen Anne Street, Harley Street, London, W.1. The house is a memorial to Dr. Edward Wilson, the devoted doctor of Scott's Antarctic expeditions, whose life is an inspiration to any medical man or woman. His brother, the Rev. Jim Wilson, is chaplain of the Guild of Health.

On the church side of the picture there is the Guild of St. Raphael, to which many devoted doctors and nurses belong. There is also greatly renewed interest in the ministry of healing of the Church, whereby ministers of religion hope to recapture the powers designated to them by Christ when He sent His disciples out "to preach the Gospel and heal the sick." While accepting the great scientific advances in medicine and surgery as God-inspired and to be fully used, they also realize that they themselves possess powerful spiritual means of healing which should be made available in the fight against disease and the maintenance of health, and be harnessed to the recognized "professional" means.

The ideal for such work would be the priest-doctor, but in the meantime it would seem reasonable to have more co-operation between ministers of religion and the medical profession. All large hospitals, and very specially mental and mental deficiency hospitals, could with great advantage have whole-time, preferably resident, padres with whom the medical staff could have conferences over cases. In general practice, also, the general practitioner might well educate his patients to call in their minister at the same time as they send for their doctor, and this with great advantage to all concerned.—I am, etc.,

Morpeth. J. H. THOMPSON.

Controlling Anticoagulant Therapy

SIR,—In the report of an inquest[1] I am quoted as saying, in connexion with "marcoumar" therapy, that "there was no agreement among doctors whether prothrombin estimations were necessary in controlling dosage." It has been suggested to me by several doctors that this statement might give rise to the impression that marcoumar differs from other anticoagulants of the dicoumarol type in regard to the need for careful control of dosage. May I take this opportunity of clearing up the matter by saying that my statement at the inquest was not intended as an expression, either of my personal opinion or of that of the firm which manufactures marcoumar, on the desirability of prothrombin testing during treatment? All information sent out by the manufacturers contains a clearly worded recommendation that treatment with the drug be controlled by means of frequent prothrombin estimations.

Whilst I believe that this recommendation is in accordance with the opinion of the majority of doctors using anticoagulants of the dicoumarol type, nevertheless a series has been published in which the dose of ethyl biscoumacetate was controlled by means other than the routine testing of the prothrombin time.[2]—I am, etc.,

London, W.1. MARGARET BRIGGS,
Medical Adviser to Roche Products, Ltd.

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1 *British Medical Journal*, May 1, p. 1045.
2 Goadby, H. (1953). *Quart. J. Med.*, 22, 517.

Carcinoma and Neuropathy

SIR,—The differential diagnosis of carcinomatous neuropathy and myopathy from dermatomyositis, polymyositis, and myasthenia gravis may certainly be difficult. I would agree with Dr. J. N. Walton (*Journal*, May 15, p. 1155) that muscle biopsy is sometimes required to help in the distinction. Professor Dorothy Russell, Dr. Marcia Wilkinson, and I have now published a detailed report[1] of the clinical and pathological findings in our series of patients with carcinomatous neuropathy and myopathy. In no case did we find pathological evidence of dermatomyositis or polymyositis.—I am, etc.,

London, E.1. R. A. HENSON.

REFERENCE

1 *Brain*, 1954, 77, 82.

Appointment with Fear

SIR,—Mr. M. Donaldson (*Journal*, May 22, p. 1208) seems to have missed the whole point of my letter (*Journal*, April 17, p. 932). The fear of cancer already exists, he says, so let us make it a bigger and better fear. I was prompted to write my original letter as an attempt to halt our own unwitting conspiracy to increase this already existing fear; to prevent additions of such comparative rarities as cancer of the mouth into the field of "cancerphobia." There isn't much left which the patient can safely do, so please allow him to put something into his mouth without the fear of dropping dead. By all means encourage the patient to talk of his fear of cancer, but don't headline a new research into some rare cancer he has never even heard about.

If some learned professor wonders what relation there is between cancer of the big toe and the price of butter, don't let the lay press get hold of the idea and publish

it in headlines. Nobody suggests that particular individuals should not do all the research they want to do into anything which takes their fancy. It is the premature presentation to the public, and method of presentation of unproved results, which is the cause of the matter. How a statement about "smoking and cancer of the mouth" at this stage could help to allay "apprehension, ignorance, and uncertainty" I really fail to see.

We cannot put the clock back, I agree, but there is no need deliberately to put it forward. There has obviously been a failure somewhere, on our part, in allowing this "cancerphobia" to develop in "nearly 100% of the population," so let's think again, examine our own fears, and find out what has gone so badly wrong in our methods, which has produced this modern mental disease. Make no mistake, we are responsible for it. It isn't the patient's attitude which needs changing. It is our own, which places the accent on organic disease to the exclusion of mental. For the greater part of the population it is the latter which is the more important, and the patient "dies a thousand deaths" instead of one. In conclusion, "Knowledge is the antidote to fear," but Emerson did not mean "knowledge" culled from kidney pill advertisements and press stunts.—I am, etc.,

London, E.9. PAUL R. SAVILLE.

Pethidine for Pain and Insomnia

SIR,—The preference shown by Drs. R. G. B. Wigoder and H. Jeffs (*Journal*, May 15, p. 1156) for using pethidine instead of morphine in the symptomatic treatment of pneumonia deserves extensive trial. This is justified by the adequate reasons given. Since we have no memory for pain, however, the following case outline is submitted, as it may add weight (if indirectly) to their thesis.

An otherwise fit labourer first attended hospital in the early morning, bitterly complaining of the pain in his right thumb. He had no sleep during the night because of this. On examination there was an extremely tender, fully developed distal pulp infection, for which immediate surgery was imperative. A general anaesthetic was, of course, recommended to the patient. This he firmly refused to have. Still, he was anxious to have his thumb "lanced." Pethidine 100 mg. was given intramuscularly, then the part was suitably prepared for incision and an ethyl chloride spray was applied to it. Deep bilateral incisions of the affected volar pad were greeted with no more protest than a gush of pus. There was no pain.

Obviously, treatment would have been impossible had not pethidine first been given. In the circumstances more could not have been required if morphine had been administered alternatively.—I am, etc.,

London, S.W.1. DUNCAN D. MACDONALD.

Single Incision for Bilateral Orchidectomy

SIR,—Mr. C. J. Cellan-Jones (*Journal*, May 1, p. 1039) looks on my recommendation of the scrotal approach to the testis as humorous. He should know from our meetings in the Middle East that I am a Scotsman, and therefore humourless. The phrase he underlines to make his point, "trim or enucleate," was used to summarize all these procedures (short of removal, in which case it is not replaced in the scrotum) to which a testis may be subjected. Enucleation through a scrotal incision is the best method of castration in the treatment of prostatic cancer.

The inguinal approach to the testis is, in my view, an example of muddled post-Listerian thinking, which looked on the avoidance of "germs" as more important than the preservation of tissue resistance. This attitude was knocked out by the experience of the first world war. The tendency of surgery to-day is to favour direct approaches where they are not traumatic, and to avoid the unnecessary dislocation of areolar planes implied in such incisions as the infra-umbilical paramedian rectus-retracting approach to the appendix.

I do not seek to convince anyone. I would only say: "Don't think; try the experiment." If Mr. Cellan-Jones was unlucky with the scrotal approach 25 years ago, he might be luckier to-day. Most of the surgeons with whom I have conversed during the recent meetings of the Association of Surgeons and the American College prefer the direct to the indirect operation.—I am, etc.,

London, N.W.8. HENEAGE OGILVIE.

Tuberculin Testing

SIR,—In regard to Dr. P. D. Mulkern's letter on the "false positive" jelly test (*Journal*, May 1, p. 1039), may I make the following observations? From experience in the general B.C.G. contact clinic, and in routine tuberculin jelly testing in residential nurseries, it was found necessary to assess the reliability of the jelly test. In a sample test the children at two residential nurseries had jelly and Mantoux tests (1/1,000 old tuberculin) at the same time. Thirty-nine children were tested, and thirty had positive jelly tests. All had negative Mantoux tests and normal chest *x* rays. At the one nursery, control jelly tests were done, and there was no suggestion of any reaction; it was also noted that the results were almost identical with two different makes of jelly used simultaneously on each child. The cause of positive jelly reactions in children who were Mantoux-negative (1/1,000) was not found, but the practical significance is clear. There is general acceptance that the jelly test is equivalent to the ten units Mantoux test.

It has been the practice at the B.C.G. contact clinic for suitability for vaccination of infants under 6 months old to be decided on by jelly testing. If the occurrence of these anomalous positive jelly tests is not realized, there will be failure to vaccinate these infants. It appears that vaccination of contact children may be the most effective application of B.C.G. vaccination in the reduction of childhood tuberculosis in this country.[1] It is most important that false positive jelly tests do not result in failure to vaccinate tuberculin-negative contact children. Experience in the general clinic substantiates the occurrence of these anomalous positive jelly reactions. In this work there was no appreciable association of a positive jelly test with a stereotyped catarrhal syndrome. A report is in preparation on the suitability of the jelly test for routine use by health visitors, and on B.C.G. vaccination of anomalous jelly-positive Mantoux-negative cases.—I am, etc.,

Birmingham. W. L. GORDON.

REFERENCE

1 Lorber, J. (1953). *British Medical Journal*, 2, 1122.

Domiciliary Obstetrics

SIR,—Your own kindly criticism (*Journal*, April 10, p. 861) of my essay on domiciliary obstetrics (p. 841) doubted whether the family doctor with consultant support but no postgraduate experience could give adequate intranatal care, but you were in no doubt about his ability to do so antenatally. Mr. C. J. Dewhurst (*Journal*, May 1, p. 1037) does not agree, for, he suggests, the newly qualified practitioner will forget to take a history, will forget that previous postpartum haemorrhage is an indication for hospital delivery, will agree to the delivery of twins at home, will be uncertain of his findings on abdominal examination, cannot diagnose a breech, and will examine cases of antepartum haemorrhage vaginally. He will attempt forceps delivery although he cannot estimate cervical dilatation, and he will not know when to ask for consultant help. To this, Mr. D. S. Greig (p. 1038) adds that general practitioners are not alert to note the onset of pre-eclampsia, and have little regard for the presence of anaemia in pregnancy.

Some would call this exaggeration. If it is not, then it is a terrible indictment of the teaching of the future general practitioner in the obstetrical departments of our medical schools. I find it difficult to agree with Mr. Dewhurst that these simple things cannot be taught, or to believe that it

is impossible to train the future family doctor to be adequate in domiciliary obstetrics; and, as the average practice produces about 30 normal cases a year, he would have a sufficient volume of work to remain adequate if all these cases remained under his care, including those now delivered in hospital for social reasons.

If it is demanded that the general-practitioner obstetrician must have postgraduate experience, the number of cases per doctor will be high enough to perpetuate the present state in which a large part of antenatal and intranatal care has to be delegated to the midwife. This may have been good enough in the past, but improvement in the future is likely to depend on close co-operation between the midwife and a doctor. If it is not with the family doctor, then it is likely to be, eventually, with a house-surgeon when general-practitioner midwifery disappears completely. Mr. Greig's figures, showing that 80% of maternal deaths in his area followed home delivery, tend, as he says, to increase the demand for hospital delivery, and serve to stampede normal primiparae into hospital beds. He does not say whether the patients who died were suitable for home delivery, and it may be, as Jameson and Handfield-Jones[1] have suggested, that too many normal cases are delivered in specialist hospitals, and too many abnormals outside them.—I am, etc.,

Gloucester. IVOR COOKSON.

REFERENCE

[1] *Lancet*, 1954, 1, 665.

Herpes Zoster and Chicken-pox

SIR,—Coexistence of herpes zoster and chicken-pox in the same patient, a further example of which was recorded by Dr. C. Spencer Whitehouse (*Journal*, May 8, p. 1097), cannot be considered excessively rare. Indeed, a search of the records of this hospital for the five years 1949–53 shows that 31 patients suffering from herpes zoster were admitted during that period, and that four patients admitted for the treatment of other diseases developed zoster at some time after admission. Of these 35 cases, 11 also developed chicken-pox, usually about 3 days, but in one case 9 days, and in another case 12 days, after the herpetic eruption. Cases of trigeminal herpes were found to be complicated by chicken-pox about twice as frequently as cases of herpes of either cervical or thoracic roots; while the ophthalmic nerve was the site of the infection in four out of five cases of trigeminal herpes complicated by chicken-pox.

Most patients in whom zoster and chicken-pox coexist are, of course, elderly persons whose immunity to chicken-pox, developed in response to infection in childhood, might be presumed to have waned with the passage of time. A precise explanation of all the well-known phenomena which seem to suggest identity, or a very close relationship between the two diseases is, one feels, most likely to be supplied by further virological studies.—I am, etc.,

London, S.E.18 C. F. L. HILL.

Animal Technicians

SIR,—I do not wish to introduce any note of acrimony into a correspondence that has already included two rather ungracious letters (*Journal*, April 24, p. 983), and I was glad to read a considered statement from the Chairman of the Institute of Medical Laboratory Technology (*Journal*, May 22, p. 1207) repudiating the extravagance of some of the views of these correspondents. However, Mr. Norman himself invites a like rebuke to that which he offers your annotator, whose ignorance of the knowledge required by present-day technicians in hospital laboratories he deplores. Might not the same be said of Mr. Norman in regard to the work of animal technicians in a research department, who are expected to handle and understand several different species of experimental animals? Hospital laboratories deal mostly with guinea-pigs on routine diagnostic tests, although small numbers of mice, rabbits, amphibia, and other species may sometimes be used; but outside this restricted field—restricted from the point of view of animal work—the animal technician may find himself with responsibilities different from, but no less exacting than, those of the medical laboratory technician.

Comparisons are odious, and your annotator should perhaps have kept off a discussion of differential status among workers in complementary fields; but he has been justified retrospectively by the resentment apparently caused by his comparisons. Respect of one for the other's job is more useful than quibbles about status. Dog does not eat dog.—I am, etc.,

London, N.W.3. W. LANE-PETTER.

Folic Acid and Pernicious Anaemia

SIR,—I was interested to see Dr. C. P. Lowther's report (*Journal*, March 6, p. 564) of a case illustrating the dangers of polypharmaceutical preparations containing folic acid, and your annotation (p. 573) on the wrong use of folic acid in pernicious anaemia.

I desire to draw your attention to the following case of mine. A girl of 18 was diagnosed in 1943 to be suffering from tropical nutritional megaloblastic anaemia on adequate grounds, including bone-marrow studies. She was doing very well for the next six years on a proper diet and maintenance therapy with liver extract. During this period she bore two children. Then someone told her that there was no need to have the periodic pricks with the advent of the new remedy, folic acid, which could be taken as tablets. Six months after she gave up the liver extract and took to folic acid alone, she was admitted in my wards with well-marked subacute combined degeneration and gross sepsis in the bladder, to which she succumbed within a week of her admission.

This case would show that the danger of precipitating neurological signs exists not only in true Addisonian pernicious anaemia but also in other megaloblastic anaemias in younger persons.—I am, etc.,

Madras. K. S. SANJIVI.

Racial and Religious Tolerance

SIR,—While sympathizing with the sentiments expressed by Dr. C. P. Seager (*Journal*, May 15, p. 1156) I can't help thinking that he does less than justice to those who imply a preference for assistants of a particular race or religion. Preference for some is different from intolerance to others. By now we all know the type of person we are likely to get on with best, and if we happen to be Badmanians with a green skin is it unreasonable that we should prefer to work with similar beings?—I am, etc.,

London, W.1. R. G. ISAAC.

Mitral Stenosis

SIR,—Dr. Paul Wood's treatise "An Appreciation of Mitral Stenosis" (*Journal*, May 8 (p. 1051) and May 15 (p. 1113)) will long be read as a Bible by all those interested in the subject. It is not an exaggeration to say that no similar work has been done in the world. On reading the paper one becomes aware of the fact that the mass of information at the author's disposal is so large that only part of it could have been published. More time will be needed for the proper digestion of that which is still to come. In the interest of the future work I would like to submit an objection and then a comment.

It is stated that there was no single instance in which primary myocardial fault was responsible for failure in mitral stenosis, but it is not disclosed how the myocardial failure was excluded—perhaps by E.C.G. It is emphatically stated that in cases of predominantly mitral stenosis the cause of heart failure is high pulmonary resistance. A table is produced in evidence, which shows that all cases of mitral stenosis with failure did have high pulmonary resistance although mitral incompetence could go into failure without the latter. The fact that high pulmonary

resistance was present does not prove that it was the *cause* of failure, because it could have been a concomitant phenomenon.

My comment is on pregnancy. Dr. Wood states: "Pregnancy aggravates the symptoms and *usually* [my italics] causes some permanent deterioration." This statement is contradicted by Dr. Paul Wood himself, because he says that in 83 mothers 140 pregnancies were recorded (probably not personal observation) and *no* symptoms developed in 97 pregnancies, while symptoms appeared in 43, which gives a ratio of 2.2:1 in favour of "no symptoms," or one could say that symptoms developed only in one-third of pregnancies. Moreover, Dr. Wood says that only 17% of pregnancies precipitated permanent disabilities, and 17% cannot be called usual. The statement then should be as follows: permanent disabilities usually do *not* develop.

This is so if we accept all Dr. Wood's figures, but in the leading article (p. 1138) we are rightly reminded that Dr. Paul Wood's cases were selected from the rather severe groups: he then obtained probably the worst results in pregnancy. It would be interesting to know how much even of this deterioration is due to the natural progress of the disease for a period of nine months without pregnancy. The table of life history (Table III) shows that once the symptoms appeared—average age 31 years—the deterioration from one severity grade to the next can be very short, from 0 months till 6 as a minimum (without pregnancy). This would apply to pregnancies after the appearance of symptoms only.—I am, etc.,

London, S.E.11. J. KOHARI.

Standard of Anaesthetics in Britain

SIR,—As the author of the *Daily Express* article referred to by Dr. Geoffrey Organe (*Journal*, May 29, p. 1267), I should like to say how much I regret any trouble which my report has caused, either to Mr. Dickson Wright or to the anaesthetists. I must point out, however, that I attended the meeting by invitation along with several other newspaper reporters, including at least one representative of the American Press, and that in my account Mr. Dickson Wright was accurately reported.

It seemed to me and to some of my colleagues that Mr. Dickson Wright's statements were not mere light-hearted asides but that he was airing a serious grievance. This was also the view of two surgeons with whom I discussed Mr. Dickson Wright's speech. I have since learned from Mr. Dickson Wright that his comments were not intended to be taken so seriously, and that he was unaware that reporters were present.

I went to much trouble to give Dr. Organe the opportunity of commenting on the speech so that his views on behalf of the Association of Anaesthetists could be given similar prominence to those of Mr. Dickson Wright. Dr. Organe could not be contacted, but I left messages for him. My statement that Dr. Organe and other anaesthetists demonstrated their machines to the visiting American surgeons was not intended to suggest that Dr. Organe was present when Mr. Dickson Wright made his remarks. I do not believe that it did, in fact, give this impression to our readers.—I am, etc.,

London, E.C.4. CHAPMAN PINCHER.

Homosexuality

SIR,—Recently I was rung up by a daily newspaper, asking my views on the Home Secretary's proposed committee on sexual crime and prostitution. Had I not been debarred from stating them, this would have been my answer: I am in favour of the Home Secretary's proposed committee, provided that, in the considerable time before it reports, the fact of its being called into existence is not taken in the slightest degree to condone homosexuality between adult males in private. It must be remembered that the word "homosexuality" has become a euphemism for the practice of mutual masturbation, intra-crural and intra-anal intercourse, and other less easily stated practices between males.

I am confident that the committee will report against any legalizing or tolerating of adult male homosexuality in private. Otherwise it will be faced with the prospect in any or every city of the churches, the schools, the youth movements, the university, the Services in barracks and and in the nearby aerodrome, and every parent, all trying to turn out clean and decent citizens, all holding that these unnatural practices are immoral or evil or deadly sin, and filthy and just as foul by whatever name they are called, while in the midst of them there might flourish two exclusive clubs—let us call them "The Wilde" and "The Gomorrah"—legally in being, open to men "above the age of consent only," with their many private rooms, corrupting men so that each has his character changed, a corruption that has a considerable degree of permanence and is passed on to others, so that chains of homosexuality are formed which may persist for generations. No responsible body of men and women could for a moment consider the possibility of creating such a state of affairs. Non-medical speakers and writers seem to have no difficulty in finding opportunities to express their views on this important and partially medical subject in the press, in B.B.C. "Any Questions?," and in so-called "brains trusts." Surely, in fairness, I should be allowed to state mine in a medical paper.—I am, etc.,

Beckley, Rye. C. G. LEAROYD.

Mondor's Disease

SIR,—Following on the article by Mr. G. M. Lunn and Mr. J. M. Potter on Mondor's disease (*Journal*, May 8, p. 1074) and on the letters of Mr. John Hosford and Dr. F. Harwood Stevenson (*Journal*, May 22, p. 1207), I would like to describe a similar case which came under my care very recently.

The patient, a married man aged 39, attended surgical out-patients on April 27, 1954, complaining of pain in the right pectoral area, most marked when reaching for an object above his head. The pain had been present for two months. There was no history of infection in the area, but he stated that in December (four months before) he had been using a brace and bit for several hours, drilling some very hard wood, and in order to get firm pressure he had pressed the butt of the drill on to his chest. He was not used to this sort of work, his own occupation being clerical. On examination, there was an ill-defined area of induration in the lower lateral quadrant of the right breast, some 1 in. (2.5 cm.) in diameter, and a plexiform mass of hard cords extending from the right axilla to the right costal margin.

Two weeks later he again came to the out-patients, and the area of induration had nearly gone. The mass of cords was still present. A biopsy of one of these cords was taken, and the report on the section is as follows: "A section of this portion of tissue showed that it was lined by a normal stratified squamous epithelium and the subcutaneous tissues were entirely normal apart from a deeply placed mass of tissue which suggested fibrous tissue. No lumen of a vessel or other evidence of an obliterated vessel was seen."

My thanks are due to Mr. C. F. Critchley for his permission to publish this case, and to Dr. J. Keall for his help with the pathology.—I am, etc.,

London, S.W.11. D. M. PAUL.

A Genetic Investigation

SIR,—We are anxious to extend a genetic investigation which is at present in progress into the rare syndrome which includes hypoplastic patellae and finger-nails. One recent description of this condition is that of Hawkins and Smith.[1] If any case is known to your readers we should be most grateful for the opportunity to do further family and linkage studies.—We are, etc.,

SYLVIA D. LAWLER.
London, W.C.1. JAMES H. RENWICK.

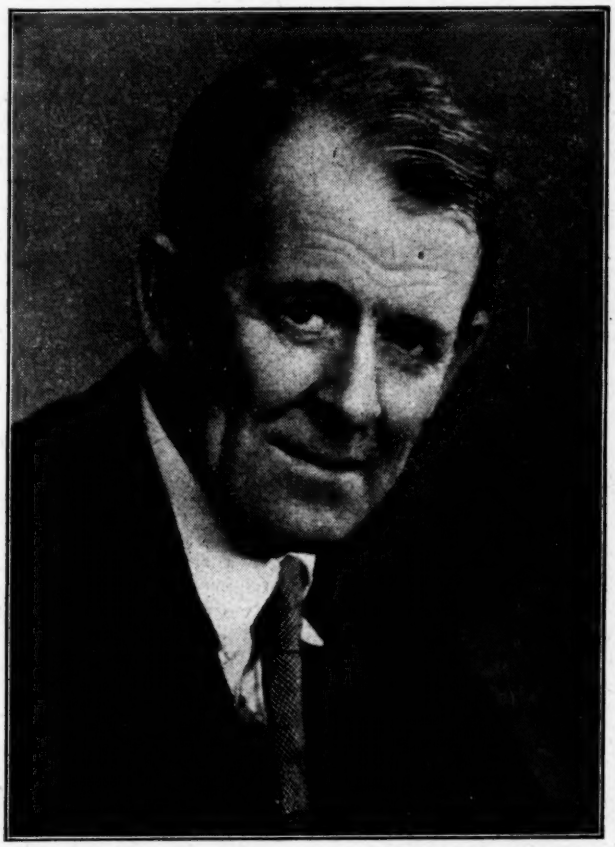
REFERENCE
1 *Lancet*, 1950, 1, 803.

Obituary

Sir JAMES SPENCE, *M.C.*, M.D., F.R.C.P.

Paediatrics has lost a leading figure and the nation a wise counsellor in the death of Sir James Spence on May 26 at the age of 62. His reputation was international, and he had made it so by hard work, clear thinking, and a happy gift of exposition which often sounded more like a fireside chat than a set lecture.

James Calvert Spence was born on March 19, 1892, the son of Magnus Spence and Isabella Turnbull, and was educated at Elmfield, York, and at the University of Durham. He graduated M.B., B.S., with honours, in 1914, just in time to enter the R.A.M.C. and serve with distinction throughout the war of 1914–18, being awarded the Military Cross and bar. An appointment at the Hospital for Sick Children, Great Ormond Street, London, followed, and this probably determined in some measure the pattern of his life, for it has been said that those who are privileged to work at this hospital are influenced by it for the rest of their lives. He then moved to St. Thomas's Hospital during 1920–2, where he held the John and Temple Research Fellowship. After this Spence went north again to become clinical pathologist and medical registrar at the Royal Victoria Infirmary, Newcastle - upon - Tyne. Biochemistry as applied to medicine was just beginning to grow, stimulated in part by Professor Hugh Maclean at St. Thomas's, under whose influence Spence had come. The scientific discipline thereby obtained was to shape his thoughts on medical education in the years to come. Next followed a year in the U.S.A. as a Rockefeller Fellow in 1926–7, mostly spent at the Johns Hopkins Hospital, Baltimore, and a return to the staff at Newcastle as a general physician. Local controversies kept him out of special paediatric work for several years, and to some extent the Babies' Hospital there was a reply to a policy which kept a man, already gaining an international reputation, off the staff of the children's hospital. Meanwhile Spence had proceeded M.D. in 1921 and had obtained the M.R.C.P. in the same year. He was elected F.R.C.P. in 1930.



[*Elliott & Fry, Ltd., London*

As his ideas matured Spence managed to achieve a remarkable synthesis between a scientific approach and a deeply humanistic outlook, the latter no doubt influenced by his Quaker origins. At meetings of such bodies as the Association of Physicians and of the British Paediatric Association, of which he was an original member and in 1950–1 president, his earliest contributions on scientific work gave place later in the case of paediatrics to a more social approach. During his chairmanship of the Social and Preventive Medicine Committee of the Royal College of Physicians of London in its early days—in the second war period under Lord Moran's presidency—there developed a growing interest in social paediatrics. His election to the Chair of Child Health in the University of Durham in 1942 was in keeping with the development of ideas in children's medicine and in tune with his own position. This was the second chair in the British Isles of this kind and the forerunner of others with similar titles in almost all the medical faculties in the United Kingdom. His choice as a medical member of the Curtis Committee was welcomed, and a great deal of the report of that committee and the subsequent legislation owed much to Spence's inspiration. He was also at this time or later a member of the medical advisory committee of the Nuffield Provincial Hospitals Trust, the Medical Research Council, the University Grants Committee, and the Central Health Services Council. In 1953 he was appointed a member of the Clinical Research Board by the Medical Research Council. The establishment of the board was one of the principal recommendations in the White Paper on "Clinical Research in Relation to the National Health Service." All this entailed much travelling, and the strain undoubtedly contributed to an illness in 1952 which necessitated a slowing down of the pace. He was greatly in demand as a lecturer, and the list of official lectureships is long, including the Bradshaw Lecture (1940), the Charles West Lecture (1946) at the Royal College of Physicians of London, the Dawson Williams Prize and Lectureship of the British Medical Association (1949), and the Linacre Lecture at St. John's College, Cambridge (1951). Abroad equally he fulfilled his role as ambassador and lecturer. He was the Inter-State Postgraduate Lecturer in Australia in 1948, and he gave the Cutter Lecture at Harvard in 1949 and the Blackader Lectures before the Canadian Medical Association in the same year. By now he was physician to the Royal Victoria Infirmary, Newcastle-upon-Tyne, with his child health department in the grounds of the hospital, to the General Hospital, and to the Babies' Hospital in that city. There he began to experiment with the admission of mothers with their babies, and so successful was this that many visitors sought out "Sir Spence," as overseas friends called him, to see exactly what was done. His knighthood had come in

1950 and was a culmination of many other honours, including an honorary D.Sc. from the University of Western Australia in 1948 and an honorary LL.D. of Cincinnatti. He was a member of the American Academy of Pediatrics and of the Canadian Society for Study of Diseases of Children.

James Spence—"Jim" to his intimates—had an attractive personality. His twinkling blue eyes and uncontrolled lock of hair gave him a faintly puckish appearance, which was reflected also in his talk. "Whimsical" is the adjective that was often used. It was often uncertain what way he was thinking, and indeed he was often a jump or two ahead of current thought and practice. A faint but friendly exasperation would sometimes develop among those associated with him, easily dissipated by the next conversation. He married in 1920 Kathleen, youngest daughter of Robert Downie-Leslie, of Aberdeen, and had one son and four daughters. His home life was friendly and charming for those privileged to share it. The holiday house in Grasmere among the mountains he loved to climb was a popular trip for those visiting Windermere for the British Paediatric Association, in the founding of which he played a notable part; and to him largely was due the happy choice of Windermere as a meeting-place. He moulded the development of the B.P.A., especially in its orientation towards social paediatrics in the war years, and was a wise elder statesman long after he had held office on its committees. His work for university education revealed a mind which was deeply steeped in tradition and humanitarianism. Whatever it was—the development of some medical department, the securing of adequate remuneration for junior lecturers in all the faculties—he was equally keen and well briefed by his personal investigations of the problem which over and over again demanded a scientific analysis and a solution which involved a deep concern for personal problems. Spence was an international figure as well as a national one, and he has left the whole community in his debt.

We are indebted to Sir HAROLD HIMSWORTH for the following appreciation: The death of James Spence has deprived British medicine of an influence that it could ill afford to lose; but it was an influence which was so largely personal that it is difficult to pay tribute to it so that future generations will understand the esteem in which he was held by his contemporaries. There are some men—the majority—who achieve eminence by building some part of the factual structure of knowledge. There are others—the architects of knowledge—who give shape to particular concepts. Both leave contributions which are evident not only to their contemporaries but to their successors. But there are yet others—a few—whose contributions lie in appreciating needs and creating the climate of opinion in which these can be translated into realizable concepts. Their influence is to be measured not in terms of the factual contributions which survive them but in the value that was placed on their advice during their lifetime. To a certain extent no man can achieve eminence in his profession without contributing in each of these ways. James Spence made his own contributions to factual knowledge. In his work for child health he developed his concept of the particular field of medicine in which he was interested. But it is probable that it was in his contribution to professional thought, of the form and shape which medicine should take to meet the needs of its own development and the society which it serves, that his influence was most pervasive and profound.

At the time of his death James Spence was serving for a second period on the Medical Research Council. That in itself was an indication of the regard in which his advice was held. He attended his last Council meeting on April 23. His advice on detail was as valuable as ever; but it was typical of him that, ill as he was, his main concern was to ventilate a problem broader even than medicine itself. He was concerned with the whole question of the relationship of scientific knowledge to the intellectual development of our society, not in any vague or sentimental sense, but as it expressed itself in the concrete problem of integrating the effort of the scientific organizations of government with that of the universities. It was this ability to appreciate the larger significance of the drift of events, and to arrest the attention of those who might influence them, that gave his advice its peculiar value. Not that he was proved always to be right. No man who attempted to foresee distant developments could hope to be. But his opinions were never negligible and, more often than not, showed a grasp that seemed almost inspired.

Foresight of this range is a talent which, in general, men appreciate only in retrospect. At the time it is seldom welcome. Perhaps the greatest tribute that can be paid to Spence as a man is that his contemporaries were prepared to heed him and yet still held him in affection. If his character had been different, he might so easily have followed the commoner lot of the imaginative and become a mere rebel. He had, however, a fundamental generosity of temperament which conditioned his attitude to others and their response to him. This, combined with a very characteristic whimsical charm, endeared him even to those with whom he was in most disagreement. To juniors he was an inspiration. His curiosity was ever alive, and he retained the capacity to see the fascination of the ordinary. But he never forgot the man behind the work; and there must be many who remember the appreciative aside which showed that the true measure of their achievement had not been overlooked. To both contemporaries and juniors alike, he was a very stimulating, very human, and most engaging colleague.

C. W. FORSYTH, M.D.

Dr. C. W. Forsyth, formerly medical superintendent of Winson Green Hospital, Birmingham, died suddenly at Capetown on May 16 while on a visit to his son. He was 77 years of age.

Charles Wesley Forsyth was born on June 28, 1876, and was educated at Owens College, Manchester, and at University College Hospital, London, where he had a distinguished career as a student. He graduated M.B., with first-class honours in anatomy, from London University in 1903, having taken the diplomas of M.R.C.S., L.R.C.P. in the previous year.

His early years were devoted to general practice, but he eventually became interested in psychiatry, and after serving in various hospitals of the London County Council proceeded to the M.D. (in mental diseases) in 1919. In the same year he was appointed deputy medical superintendent of Hollymoor Hospital, Northfield, Birmingham, and in that post was able to develop his undoubted clinical ability to the full. These qualities led to his promotion to the position of medical superintendent of Winson Green Hospital, an appointment he held until his retirement through ill-health in 1938.

On the academic side, too, Dr. Forsyth had a distinguished career, being lecturer, clinical lecturer, and examiner in psychological medicine at Birmingham University from 1932 until his retirement. The years covered by his tenure of office at Winson Green saw a steady development of the active treatment of mental illness, and alongside this, and indeed arising from it, an extensive programme of modernization of the hospital. In the inception of that programme Dr. Forsyth was personally responsible, and it constitutes a memorial to his energy and enthusiasm.

Aside from his purely medical interests his principal hobbies were gardening and cricket. Evidence of the former is to be seen in the layout of the hospital grounds, which are in striking contrast to the industrial surroundings; while as a keen cricketer he was responsible for the recruitment to the hospital staff of many sportsmen who later, under his guidance and tuition, became equally competent male nurses. Dr. Forsyth leaves a widow and a son, to whom we extend our sympathy in their loss.—J. J. O'R.

W. J. WILSON, M.D., D.Sc., LL.D., D.P.H.

By the death on May 6 of Professor W. J. Wilson, emeritus professor of public health in Queen's University, the Belfast Medical School has lost one of those who played an important part in its growth and development. He was 74 years of age.

Born at Straid Mills, Co. Antrim, on August 23, 1879, William James Wilson was educated at the Royal Belfast Academical Institution and at Queen's College, Belfast, then a constituent college of the former Royal University of Ireland, and there he had a brilliant career. He won the Henry Hutchinson Stewart Scholarship in anatomy and physiology of the University for 1901–2, graduating B.A. with first-class honours in the latter year. He secured first place in the final M.B., B.Ch. examination in 1905, again passing with honours, and two years later he proceeded to the M.D., gaining a gold medal for his thesis. In 1906 he obtained the Cambridge D.P.H. and won the studentship in pathology and bacteriology of the Royal University of Ireland, and four years later he took the degree of D.Sc. of Queen's University. Earlier, while at Queen's College, he won the senior scholarship in chemistry in 1902 and the Dunville Studentship in the following year.

After a period of postgraduate study in Berlin, Wilson returned to Queen's as Riddell demonstrator in pathology and joint lecturer in sanitary science, and it was in the latter subject that he made his greatest contribution to the University and to medicine in general. Under his guidance his joint lectureship grew into an independent department of public health, and in 1921 he was appointed to a chair in the subject. He retired from the chair in 1948 and was appointed emeritus professor; later, the honorary degree of LL.D. of Queen's University was conferred upon him.

Wilson early became interested in the improvement of bacteriological culture media, and before the first world war he made several contributions in that field. In this period, too, he described the presence of antibodies in the blood of patients with typhus fever, which had the power to agglutinate some coliform organisms, and thus paved the way for the development of the Weil–Felix reaction. After the war he continued his search for selective culture media, and with Dr. E. M. McV. Blair eventually developed the Wilson–Blair glucose - sulphite - iron - bismuth - brilliant green medium in the examination of sewage for the presence of *Salm. typhi*, a method which has proved itself of such value in public health bacteriology. In the first world war he served with the R.A.M.C. with the rank of major and continued his bacteriological studies. From 1914 to 1917 he was specialist sanitary officer and inspector of tetanus for the Belfast military district. He was one of the first to describe Zenker's hyaline degeneration in the muscles in the influenza epidemic of 1918. On returning to civilian life he was appointed bacteriologist to several public authorities and took over the care of the water supply of Belfast, in addition to his university duties. Through such appointments he gave much service to the community at large.

Busy as he was on routine work, Wilson continued his interest in research. He also gave freely of his time to administrative matters. From 1928 to 1943 he was Dean of the Faculty of Medicine, and in that position was concerned with the welfare of the medical school in the early years of the last war. Many graduates and students owe him a deep debt of gratitude for his wise guidance in time of trouble and for his amiable interpretation of rules and regulations. A member of the British Medical Association for 48 years, he acted as one of the honorary secretaries of the Section of Pathology when the Association held its Annual Meeting at Belfast in 1909; at the Nottingham Meeting in 1926 he served as a vice-president of the Section of Public Health; and at Belfast in 1937 he was president of the Section of Hygiene and Public Health. He was also president of the Ulster Medical Society in 1934–5, and from 1942 to 1945 he represented Queen's University on the General Medical Council. He was appointed a member of the University Senate, and for over 20 years was a governor of his old school, being elected chairman of the board in 1942. When the Northern Ireland Tuberculosis Act was passed in 1946 he became a member of the Tuberculosis Authority.

As the years passed, "W. J.," as he was familiarly known, became more and more a character identifying in himself the Faculty. Though a quiet man, he could be roused to battle on behalf of his medical flock and through sheer persistency accomplished much for all. By his personality, hard work, and unity of purpose he has left his name deeply engraved on the annals of the University and on the medical life of Northern Ireland. He leaves a widow, a daughter, and three sons, who are members of the medical profession.

The death of Dr. DOUGLAS J. NICOL on May 8 at the age of 59, after a long period of ill-health, has deprived Birmingham of a much-loved general practitioner and the St. John Ambulance Brigade of one of its most distinguished surgeons. Douglas John Nicol was born in Glasgow. The first world war interrupted his medical studies at Glasgow University and he served as a captain in the Highland Light Infantry from 1914 to 1917, being awarded the Military Cross. He then returned to Glasgow University, where he graduated M.B., Ch.B. in 1919. After holding the appointments of house-physician and house-surgeon at the Royal Southern Hospital, Liverpool, he settled in practice in Birmingham, where he spent the rest of his life. His war-time experiences having shown him the great importance of skilled first aid to the wounded, he joined the St. John Ambulance Brigade as a divisional surgeon in 1923, being promoted corps surgeon in 1938 and county surgeon three years later. He did outstanding work as an instructor in first aid to the police and fire brigade, and later he advised the British Electricity Authority and other nationalized industries on first-aid training. It was indeed as a teacher of first aid that Nicol made his greatest contribution. He was one of the pioneers of the new spirit of realism in first-aid competitions in which "patients" were not only made up to represent the actual injuries from which they were supposed to be suffering, but were also trained by him to behave as though they really were injured. The effect on first-aid teams was unmistakable, and the value of the experience gained was shown in their greatly improved approach when actually called upon to deal with an accident. This encouraged

Nicol to extend the realism to the basic first-aid training in the "black book." He devised a series of what he termed "little cases," and these, carefully prepared and admirably demonstrated, served to teach the essential do's and don'ts of first-aid. Candidates were often nervous of meeting him, but they realized that to be examined and passed by Nicol was to be indeed an efficient first-aider. He demonstrated his methods to many hundreds of St. John surgeons and lay members all over the country. As a visiting industrial medical officer Nicol realized the great importance of the provision of efficient first-aid training to the responsible persons in charge of first-aid boxes in the thousands of small factories in Birmingham, and during his years as chairman of the St. John Ambulance Association in that city he had the joy of seeing hundreds of men and women so trained and to receive the valuable support of the public health department, the Birmingham Accident Hospital, the Factory Department, and many industrialists. For these services he was promoted Commander of the Order of St. John, an honour rarely given to anyone below the rank of county commissioner. A somewhat shy and dour manner hid a kind and understanding heart, for one had only to hear his patients praise him to realize what a tower of strength he was to them in their times of serious illness and anxiety. He had a very high professional standard and never allowed his outside activities to encroach upon his practice. Dr. Nicol leaves a widow, who is the St. John County (Nursing) Superintendent for Birmingham and who ably assisted him in all his work, a daughter, and two sons, one of whom is following his father's profession.—J. G. B.

Medical Notes in Parliament

HOSPITAL JUNIOR MEDICAL STAFF

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) discussed the shortage of resident medical staff in hospitals in the House of Commons on May 28. He asked what were the reasons for the shortage of junior medical staff in the smaller hospitals. The main factor, he thought, was that those seeking hospital appointments preferred the larger hospitals because there they gained a wider clinical experience; another factor was that in the larger hospitals they worked as members of a team. The second choice of applicants was for the most pleasant parts of the country, such as seaside resorts. Applicants went either for rich experience or a good holiday. Who could blame them, since the salary was the same in all hospitals? The salary itself was an important factor, for junior appointments in hospitals were less profitable than national service in the R.A.M.C. and in strong contrast with assistantship in general practice.

Dr. Broughton also suggested that the recent substantial increase in the number of actions for negligence brought against junior house staff was having an effect in deterring recently qualified men and women from undertaking duties which exposed them to the danger of such charges. Would the Minister consider allowing beds to be used for patients under the care of the general practitioners?

Miss PAT HORNSBY-SMITH, the Parliamentary Secretary, replied that various methods had been tried during the past two years, and some progress had been made, but the causes were very deep, and were not capable of immediate solution. The two main features were supply and demand on the one hand and fair distribution of the available staff on the other. The supply of junior hospital staff fell short of the maximum establishment by something under 10%. The check on establishment had meant that, while the teaching and large hospitals had no difficulty in getting staff, there was a trickle to the more needy and in some ways less attractive hospitals. The priority needs of the small hospitals, it was felt, should come first, and this policy had already brought results.

The most difficult problem was in distribution, and it was particularly felt at the peripheral hospitals, especially those dealing with a narrow range of work. The cause was not any decrease in supply, but a substantial increase in demand, often due to the upgrading of the smaller local hospitals with additional specialties. From the record of claims in the Ministry they had no evidence that claims for damages arose more particularly in respect of the peripheral hospital than elsewhere.

It was not practicable to increase the number of qualified doctors. There were about 2,000 a year. The number of probable vacancies in "career" posts appeared to be fairly well balanced in relation to intake, which a little while ago was a source of great concern. They could not reduce the number of doctors called up; apart from the undesirability of treating doctors exceptionally, the Services could not do without them. The most hopeful lines were to encourage general practitioners to work in hospitals, and to encourage men returning from national service to enter the hospitals for a period rather than go straight into general practice. The additional payment of £50 a year for house officer posts that were difficult to fill had not been found an efficacious method—it tended to "blacklist" a hospital; and the Ministry looked with considerable reserve on the idea of incentive pay for what should be a comparable job, and also on any suggestion that posts should be graded above their true worth.

Hospital Resident Officers

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) asked the Minister of Health what was the total number of resident medical officers in hospitals in England and Wales, and how far this was below the establishment figure. Mr. IAIN MACLEOD, replying on May 26, said the information was not available in that form, but at the end of 1953 there were in the hospitals the whole-time equivalent of 7,815 medical officers other than specialists and senior registrars, compared with an establishment in December, 1952, of 8,499.

Dr. BROUGHTON also asked what means were available to regional hospital boards and hospital management committees for filling vacancies in the resident medical staffs of hospitals. Mr. MACLEOD said that the usual method was advertisement in the medical press, supplemented as necessary by direct contact with medical schools and other appropriate bodies and persons.

Pay in the R.A.M.C.

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) asked the Secretary of State for War on May 25 what was the rank and the pay of a registered medical practitioner on joining the Royal Army Medical Corps for the period of national service, and after one year's service; and how far it was possible for a medical officer to hold higher, acting rank, with pay, during the period of national service. Mr. A. HEAD stated that a doctor was commissioned in the rank of lieutenant and got basic pay of £401 a year. After one year he was promoted captain and got £511 a year, and after a further six months £593 a year. He might get temporary promotion to the rank of major, and there were 20 National Service officers holding this rank: the basic pay was £785 a year in the first 18 months' service and £912 a year in the last six months. In addition to basic pay, marriage allowance of £117 a year for an officer under 25 and £228 a year if he was older, and specialist pay of £73 a year, were paid where appropriate.

Dr. BROUGHTON also asked what was the annual cost to the War Office of advertising to invite applicants for commissions in the R.A.M.C. Mr. HEAD said that up to last year advertising was mainly for specialists and the yearly cost was under £300. Last year just under £1,000 was spent on special publicity for the new terms of service of officers of this corps.

Cost of Training Students

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) asked the Minister of Education on May 24 what was the annual

cost to her department for the education and training of medical students in the medical schools of England and Wales. Miss FLORENCE HORSBRUGH stated that the number of students taking medical courses in the current academic year with grants from the department was 1,948, of whom 1,121 held State scholarships and 827 held awards under the Further Education and Training Scheme. She estimated the cost in fees and maintenance for the year at approximately £574,000. In addition, the department admitted for grant the expenditure of local education authorities on making awards to students taking medical courses; but the returns of the authorities did not enable her to isolate this expenditure from their other expenditure on awards.

Tracing Trichinosis

Mrs. ELIZABETH BRADDOCK (Liverpool, Exchange, Lab.) asked the Minister of Food if he was aware that, in the outbreak of trichinosis in Liverpool recently, it was found to be impossible to trace the infected pig beyond the abattoir; and, in view of the serious infection which could be caused, what steps he was taking to have complete records of the movement of pigs available to medical officers of health responsible for tracing infections. Dr. CHARLES HILL, the Parliamentary Secretary, replied on May 26 that the movement of pigs was subject to the provisions of the Movement of Animals (Records) Order, 1925, which required records of movements to be kept in a prescribed form; this order was enforced by the local authorities responsible under the Diseases of Animals Act, 1950, and the records should be available to medical officers and others when tracing infections. He also said that he shared the concern about the Liverpool outbreak. In only two of the 89 cases was the infection traced to pork, and in those cases difficulty was experienced in tracing the infected pig back to the piggery. He was looking into those cases. In the remaining cases the infection came from sausages, and it was extremely difficult in a large sausage-factory to trace a carcase.

Television Advertising

In the resumed debate in committee on the Television Bill on May 31 Dr. EDITH SUMMERSKILL (Fulham, West, Lab.) moved an amendment to prohibit the advertisement of articles recommended as medicines. She said the purpose was to protect a small section of the community against the glib patter of the salesmen who represented the drug firms. An unscrupulous advertiser might play upon their fears with some worthless preparation.

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) said that the societies and associations in the medical profession would soon be creating an unholy row if doctors found their time was being wasted in having to explain to patients that these preparations were not as good as they were said to be, or that doctors could not prescribe them.

Mr. L. D. GAMMANS (Assistant Postmaster-General) said that all would agree with the spirit behind the amendment, but the authority already had sufficient powers. The standards laid down by the advertising bodies were very rigorous, and the advertising interests had volunteered to set up an advisory committee. The B.M.A. had volunteered to nominate representatives to sit on the committee. This method would provide a most effective safeguard against abuse.

The amendment was withdrawn.

Medico-Legal

ACTION AGAINST GENERAL PRACTITIONER FAILS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On May 14, 1954, Mr. Justice Cassels gave judgment for the defendant, Dr. R. K. R. Henry, in an action brought against him by Mr. F. Sadler alleging that the death of his daughter, Kathleen Sadler, was due to Dr. Henry's negligence. Kathleen Sadler, a single woman aged 26, had died on April 27, 1952, from acute meningitis due to suppurative otitis media, and the plaintiff's case was that Dr. Henry had been negligent in failing to diagnose otitis media or treat her for it; to recognize the symptoms of meningitis; to pay attention to a swelling behind the right ear; to examine the retinae; to consider or advise operative treatment or the administration of penicillin; or to send her to hospital until too late to save her life.

On Thursday, April 24, at about 10.45 p.m. Miss Sadler, who a day or two before had had a cut in her arm sutured at Barnet Hospital but was otherwise in good health, complained to her fiancé of pain in her right ear. In December, 1950, she had had wax syringed from her ears but otherwise had no previous history of ear trouble. Next day she complained to her fiancé of pain and told him she had been up all night. Between 9 and 10 a.m. she went to see Dr. Henry at his surgery, gave a history of having had a cold earlier, and complained of earache. Dr. Henry examined her ear with an auriscope, took her temperature, which was 99° F. (37.2° C.), looked and felt behind her ear, and saw partial inflammation of the right eardrum. He saw no discharge or sign of perforation, diagnosed "catarrhal drum," and prescribed drops to relieve the pain and a sedative. He told her to see him again after the weekend but if the condition did not resolve within 24 hours to call and tell him.

That evening she was restless and in pain from her ear, which discharged blood and pus, and she vomited during the night. On Saturday morning Dr. Henry was called, and saw her at about 11 a.m. He removed the stitches from her arm. He was told she had had a headache and some vomiting, and that she had "rushing noises like the sea" in her head. He again examined her ear through the auriscope and thought it slightly improved. He saw no discharge nor bulge at the drum nor perforation, and was not told that there had been a discharge. She seemed worried about her arm and he ascribed the vomiting to her nervous condition. He saw no indication of suppurative otitis, nor anything such as neck rigidity to indicate meningitis. Her temperature was still 99° F. and she talked rationally. He ordered glucose and codeine tablets.

On Sunday morning she vomited back a cup of tea, and there was discharge from her ear and some nose bleeding, but she said she felt better. At 12.15 p.m. she asked for the curtains to be drawn because she did not like the light. At 2 p.m. she vomited again and complained of her head. At 3 p.m. she complained of loss of use of her legs, and that her fingers felt funny. At 6.30 p.m. Dr. Henry called and made a thorough examination. He found her ear clean and that she could move her legs, and he could find nothing clinically wrong. Her temperature was again 99° F. and she was worried and emotional. He saw no signs of irrationality, no discharge from the ear, no perforation of the drum, no swelling, and no rigidity of the neck. He thought she had acute hysteria, and recommended her family not to fuss her.

At 8.45 she became irrational and Dr. Henry, communicated with by telephone, arranged for her admission to hospital. At 11.50 p.m. she died, almost immediately after admission.

At necropsy the mastoid cells were found to be full of pus. The eardrum had a small perforation at the back of a diameter of 1/32 in. (0.8 mm.), and the tegmen tympani had become eroded and was perforated by a hole 1/16 in. (1.6 mm.) in diameter resulting in fulminating meningitis, giving rise in turn to uncus herniation, which was the immediate cause of death.

The principal complaint against Dr. Henry put forward by the expert witness, Mr. T. E. A. Stowell, called for the plaintiff, was that on the Saturday he ought to have used an ophthalmoscope, and would then have seen early changes of optic neuritis, indicating meningitis; and that while neck rigidity may not have been present on Saturday morning it must have been by the afternoon. He conceded that on Saturday morning the usual symptoms of otitis media and meningitis were probably masked.

The expert witnesses called for the defence were Mr. Terence Cawthorne, Dr. Denis Williams, Dr. A. H. Douthwaite, and Dr. J. C. Gregory, a general practitioner. The defence's evidence was that the condition found at necropsy was consistent with no neck rigidity whatsoever

before death, and that there were no signs or symptoms present early enough to enable a reasonably careful doctor to take action to prevent death. Fatal brain infections could occur with no warning signs or symptoms at all.

Mr. Justice Cassels found that there were no signs or symptoms which could reasonably have led Dr. Henry to suspect localized meningitis. His diagnosis of hysteria was as it turned out a mistake, but one which others might well have made in the circumstances. He therefore gave judgment for the defendant, saying that Dr. Henry impressed him as a careful general practitioner who had failed in the difficult circumstances of the case to diagnose the real condition, which the necropsy disclosed. That did not prove him negligent, and he was entitled to return to his practice with a clear conscience.

The Medical Defence Union instructed Messrs. Hempsons to act for Dr. Henry. The defendant's costs of the action, which lasted 13 days, were about £3,500, but the M.D.U. was unable to recover them because the plaintiff was without means and had brought the case under the free legal aid scheme.

Vital Statistics

Week Ending May 22

The notifications of infectious diseases during the week included pneumonia 520, scarlet fever 832, whooping-cough 2,419, diphtheria 22, measles 1,940, dysentery 1,104, acute poliomyelitis 25, paratyphoid fever 4, and typhoid fever 3.

Infectious Diseases

In England and Wales during the week ending May 15 the largest variations in the number of notifications were increases of 279 for whooping-cough, from 2,381 to 2,660, 179 for scarlet fever, from 719 to 898, and 83 for dysentery, from 948 to 1,031.

The largest rises in the trends of whooping-cough were 59 in Lancashire, from 219 to 278, 47 in Warwickshire, from 122 to 169, and 45 in Yorkshire West Riding, from 156 to 201. A small rise in the incidence of scarlet fever occurred throughout the country; the largest was 39 in Lancashire, from 91 to 130. 1,706 cases of measles, 28 fewer than in the preceding week, were notified. The only variations of any size in the local trends of measles were a fall of 57 in Staffordshire, from 195 to 138, and a rise of 56 in Lancashire, from 355 to 411. 9 cases of diphtheria were notified, being the same as the record low level of the preceding week. 3 cases were notified in Lancashire and 3 in Warwickshire, Birmingham C.B. 4 of the 7 cases of paratyphoid fever were notified in Staffordshire, Burton-on-Trent C.B.

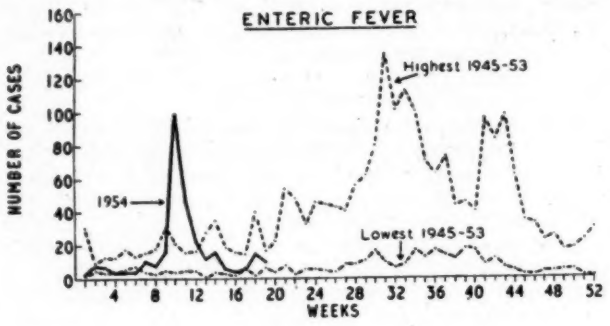
19 cases of acute poliomyelitis were notified. These were 1 fewer for paralytic and 3 fewer for non-paralytic cases than in the preceding week. 4 cases occurred in Essex and 2 cases in Gloucestershire, Staffordshire, Lancashire, and Yorkshire West Riding.

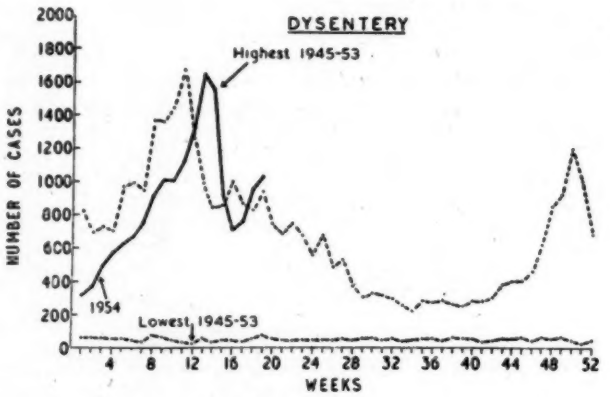
The largest rises in the number of notifications of dysentery were 59 in Yorkshire West Riding and 46 in London. The largest returns were Lancashire 272 (Stretford M.B. 54, Irlam U.D. 37, Rawtenstall M.B. 24, Bolton C.B. 21, Liverpool C.B. 20, Salford C.B. 18, Swinton and Pendlebury M.B. 16, Eccles M.B. 14, Manchester C.B. 13, Denton U.D. 12), Yorkshire West Riding 177 (Dewsbury C.B. 59, Sheffield C.B. 45, Baildon U.D. 10), London 153 (Islington 38, Lewisham 23, Deptford 10), Leicestershire 49 (Leicester C.B. 45), Sussex 38 (Uckfield R.D. 19, Brighton C.B. 16), Middlesex 33, Cheshire 33 (Ellesmere Port U.D. 21), Warwickshire 29 (Birmingham C.B. 14), Nottinghamshire 28 (Beeston and Stapleford U.D. 15), Staffordshire 26, and Gloucestershire 22 (Bristol C.B. 21).

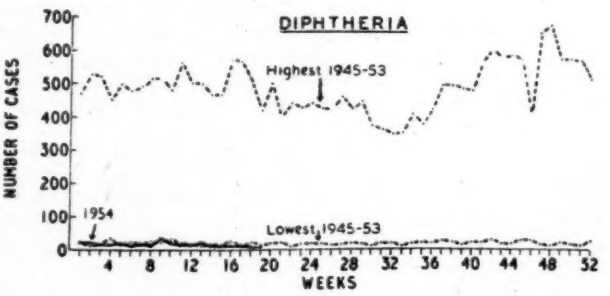
In Scotland the notifications of dysentery rose from 311 to 335. The largest returns were Glasgow 226, Lanark county 20, Dundee 19, and Edinburgh 17.

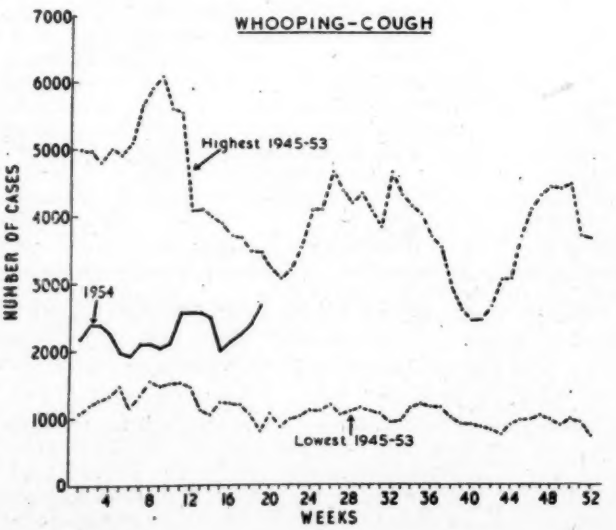
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 15** (No. 19) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	9	0	4	1	2	17	1	12	0	3
Dysentery	1,031	153	335	6	1	736	119			9
Encephalitis, acute	5	0	0	0		4	0	1	0	
Enteric fever:										
Typhoid	3	1	0	0	0	2	0	0	1	
Paratyphoid	7	0	1	0	0	11	2	1 (B)	0	
Food-poisoning	240	22		0		234	21		0	
Infective enteritis or diarrhoea under 2 years				8	20				19	17
Measles*	1,706	58	169	121	332	10,034	305	492	355	245
Meningococcal infection	35	5	15	0	1	43	3	11	1	
Ophthalmia neonatorum	29	4	12	0		47	7	10	1	
Pneumonia†	463	35	196	5	2	515	29	192	7	4
Poliomyelitis, acute:										
Paralytic	14	0	2	1		25	5	0	0	3
Non-paralytic	5	1				11	1			
Puerperal fever§	258	43	14	1		254	15	6	1	
Scarlet fever	898	54	110	32	43	1,286	68	174	30	62
Tuberculosis:										
Respiratory	816	91	170	21				165	33	
Non-respiratory	118	6	26	3				39	5	
Whooping-cough	2,660	85	308	47	39	3,312	244	480	50	153

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0		0
Dysentery	0	0		0		0	0			
Encephalitis, acute		0	0		0		0			0
Enteric fever	0	0	0	0		0	0	0		
Infective enteritis or diarrhoea under 2 years	9	0	1	1	0	9	0	0	1	3
Influenza	10	2	0	2	0	10	2	0		3
Measles		0	0	0	0		0	1		1
Meningococcal infection		0	0				0	0		
Pneumonia	200	41	25	19	9	209	17	9	11	6
Poliomyelitis, acute	0	0	0		0	1	0			0
Scarlet fever		0	0	0	0		0	0		0
Tuberculosis:										
Respiratory	86	11	1	2	9	100	14	16	1	7
Non-respiratory			1	0	2		1	1	0	6
Whooping-cough	2	0	0	1	0	1	0	1	0	0
Deaths 0–1 year	249	28	30	8	17	220	23	30	5	15
Deaths (excluding stillbirths)	5,441	755	637	139	180	4,861	677	526	102	203
LIVE BIRTHS	8,016	1216	962	235	445	8,411	1257	932	235	462
STILLBIRTHS	207	21	24			205	25	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Opening of New Institute of Urology.—The new building of the Institute of Urology in Henrietta Street, Covent Garden, just opposite St. Peter's Hospital, was opened by Viscount WAVERLEY on June 1. The Institute is an adapted house dating back to Caroline days. It now contains a museum and lecture room, laboratories, library and reading-room, a photographic studio, and a records department. Viscount Waverley said that the inauguration of these premises was an important step towards realizing the conditions which must be fulfilled if the Institute were to remain a recognized unit of the Postgraduate Medical Federation. The ideal arrangement would be proximity to a large teaching hospital, but that was unattainable at present. St. Peter's, which had engaged in postgraduate training of urological surgeons as long ago as 1860, and St. Paul's which had taken a share in this work since 1928, were fairly close together, and the Ministry had also given ward accommodation at St. Philip's. The Institute now had available 138 beds in three separate buildings within easy reach. This should make possible the fundamental researches on which the Institute must rely to attract young workers interested in the academic aspects of urology.

New Chairman of W.H.O. Executive Board.—Dr. HENRY VAN ZILE HYDE, chief of the Division of International Health of the United States Public Health Service, has been elected chairman of the World Health Organization executive board for the coming year. He succeeds Dr. Melville Mackenzie. Dr. Hyde was born in Syracuse, New York, in 1906, and studied medicine at Yale and Johns Hopkins. Before turning to public health he was for several years in private practice. During the last world war he served in the Middle East, and subsequently was in charge of six U.N.R.R.A. refugee camps in that region. In 1945 he was appointed assistant chief of the Health Branch of the U.S. Department of State, and since then has been engaged in various capacities in international health affairs.

Westminster Hospital.—The old students dinner of the Westminster Hospital and Medical School was held at Grosvenor House on May 28 with Mr. A. GOODWIN, F.R.C.S., in the chair. In proposing the health of the hospital and the medical school Mr. Goodwin referred to the great loss sustained by the hospital in the untimely death of Dr. J. L. Lovibond. In giving the toast "The Guests," Dr. G. GARMANY, in a refreshingly witty speech, illustrated how a psychiatrist should tackle this familiar theme. Sir JOHN CHARLES responded. Mr. A. C. H. BELL, F.R.C.S., proposing the health of the chairman, said that he would always be remembered with deep affection by his colleagues; Mr. Goodwin was a great teacher and a first-class surgeon, and they all regretted his approaching retirement from the hospital staff. In his reply Mr. GOODWIN entertained the company with his reminiscences as a big-game hunter.

Clinical Research Unit at Glasgow.—The Secretary of State for Scotland, Mr. JAMES STUART, opened a new building at the Western Infirmary, Glasgow, for the Medical Research Council's clinical chemotherapeutic research unit. He described the building, which cost £50,000 and was paid for by the Western Regional Hospital Board for Scotland, as the first specially designed research unit to be built in Scotland since the war. The clinical chemotherapeutic research unit was established in 1946, under its present director, Dr. James Reid, and has been concerned mainly with the development and investigation of drugs for the treatment of rheumatic disorders. Until recently the unit was housed at the Gairdner Institute of Medicine. Other speakers at the opening ceremony included Sir HAROLD HIMSWORTH, secretary of the Medical Research Council, Sir HECTOR HETHERINGTON, principal of Glasgow University, Sir ALEXANDER MACGREGOR, chairman of the Western Regional Hospital Board, and Dr. REID.

Scottish Research Committee.—The following new appointments have been made by the Secretary of State for Scotland to his Advisory Committee on Medical Research: Professor R. W. B. ELLIS, Department of Child Life and Health, University of Edinburgh; Professor R. J. KELLAR, Department of Obstetrics and Gynaecology, University of Edinburgh; Professor R. B. HUNTER, Department of Materia Medica, University of St. Andrews; Professor W. M. MILLAR, Department of Mental Health, Aberdeen University; Professor C. M. YONGE, F.R.S., Department of Zoology, University of Glasgow. The chairman of the committee is Sir EDWARD APPLETON, F.R.S. They advise the Secretary of State on the initiation, direction, co-ordination, and conduct of medical research.

District Nursing in London.—Sir ZACHARY COPE was elected chairman of the Central Council for District Nursing in London at the annual meeting at County Hall on May 27. There had been great changes, he said, in the nurse's position during the last 50 years—changes in training, accommodation, remuneration (5s. to 10s. a week was the salary in 1905), and status. The changes were still continuing. Possibly the work of the district nurse had changed less than that of other branches of the profession, because, while the hospital nurse was to a certain extent tending to become more administrative, the district nurse was still primarily engaged in the actual nursing of the sick. She was closer to the patient than any other class of nurse, and often had to be the adviser, confidante, and friend as well. She was the "general practitioner of the nursing world." It was very necessary, continued Sir Zachary, that there should be more integration of the nursing services of the country, so that patients leaving hospital could receive proper care and attention, while the use of hospital beds for some patients who could quite well be nursed at home would be saved. Too often after patients left hospital their condition deteriorated owing to lack of aftercare.

Conference of Prison Medical Officers.—The annual conference of prison medical officers and psychologists was held at the Home Office on May 28. Dr. H. K. SNELL, Director of Medical Services, Prison Commission, was in the chair. Dr. D. S. MACPHAIL and Dr. R. C. SIMPSON, visiting psychotherapists at Wormwood Scrubs Prison, spoke on "Psychotherapy in Prison and Advances made in Group Treatment." In the afternoon Dr. A. A. S. MCDONALD, Medical Officer, H.M. Prison Parkhurst, and Dr. M. R. P. WILLIAMS, Medical Officer, H.M. Prisons Bristol and Leyhill, read papers on "Some Medical Aspects of Long-term Imprisonment." The papers were followed by discussions. On May 29 the psychologists held a separate session.

Treponematosis Award.—An international award to honour outstanding workers in the field of venereal diseases and non-venereal treponematoses is planned. It will be administered by the W.H.O. and will consist of a bronze medal and a scroll. Individuals and organizations are invited to contribute. Cheques should be made payable to "The International Treponematosis Award Fund," and sent to Dr. R. R. WILLCOX, St. Mary's Hospital, London, W.2.

Colyer Medal.—Last year the Faculty of Dental Surgery of the Royal College of Surgeons instituted a medal for outstanding work in dentistry, in honour of Sir FRANK COLYER. The first award of the medal will be made to Sir WILLIAM KELSEY FRY at the annual meeting of the Faculty on July 16, for his work on maxillo-facial surgery.

Naval Awards.—Surgeon Commander D. D. STEELE-PERKINS, R.N., has been appointed C.V.O. and Surgeon Lieutenant-Commander A. P. M. NICOL, R.N., has been appointed M.V.O. (5th Class). These medical officers held appointments in the *Britannia* and the *Gothic* during the recent royal tour.

Medical Golfing Society.—At the summer meeting on May 27 Dr. A. J. MAY won the Lancet Cup with a score of 73. Dr. LESLIE HARTLEY was the winner of the Henry Morris Cup, 4 up.

Professor L. J. Witts, of Oxford University, has been elected an honorary member of the Danish Society of Internal Medicine and of the Association of American Physicians.

Dr. J. Greenwood Wilson, medical officer of health of Cardiff, has been appointed chairman of the Royal Sanitary Institute's standing committee on the hygiene of food.

Dr. J. L. A. Grout, honorary lecturer in radiology at Sheffield University, is to receive the honorary degree of M.D. from the University on July 3.

COMING EVENTS

Commonwealth Tuberculosis Problems.—The N.A.P.T. will hold an open meeting on June 11 at 6.30 p.m. in the Old Library, B.M.A. House, London, when the following speakers will describe tuberculosis work in their countries: Dr. A. R. SOUTHWOOD, Director General of Public Health, South Australia; Mrs. A. SONI, medico-social worker, India; Dr. S. C. HAWES, of New Zealand. Details from N.A.P.T., Tavistock House North, Tavistock Square, London, W.C.1.

Stewart Lecture.—Professor G. R. CAMERON, F.R.S., will deliver the first Matthew Stewart Lecture at Leeds on June 17. His subject will be "The Exploration of the Cell." The lecture will take place in the Littlewood Hall of the General Infirmary at 4 p.m.

Bakerian Lecture.—Professor A. R. TODD, F.R.S., will deliver the Bakerian Lecture to the Royal Society on June 17 at 4.30 p.m. His subject is "Chemistry of the Nucleotides."

Cambridge Graduates Medical Club.—The annual general meeting of this club will be held at Emmanuel College on Friday, June 25, at 7 p.m., followed by a dinner at 7.30 p.m. at an inclusive price of 32s. Those intending to be present should send their names and the names of their guests, with a cheque, to Dr. T. B. ANDERSON, 1, Huntingdon Road, Cambridge, not later than June 10.

NEW ISSUES

Abstracts of World Medicine.—The June issue (Vol. 15, No. 4), which is now available, contains abstracts of important papers drawn from medical and other scientific journals published in some 20 different countries and in all five continents. The subjects covered range over the whole field of clinical medicine and include pathology, bacteriology, pharmacology, and chemotherapy; there are also sections dealing with medical genetics, public health, industrial medicine, anaesthetics, radiology, and history of medicine.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; a specimen will be sent free on request.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 7

EDINBURGH UNIVERSITY.—At Physiology Class Room, University New Buildings, 5 p.m., Dr. D. J. Guthrie: The School of Salerno: Systematic Teaching.

Tuesday, June 8

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. B. F. Russell: Pyococcal Infections.

●INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. Macdonald Critchley: Migraine and the Vascular Neuralgias.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 3 p.m., Professor J. Louw (Capetown): Vesico-Vaginal Fistulae.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Ophthalmology Lecture by Professor A. Sorsby: Nature of Refractive Errors.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Almroth Wright Lecture by Sir Edward Mellanby, F.R.S.: Some Actions of Vitamin A as a Controller of Structure and Function of Tissues.

Wednesday, June 9

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. Barbara M. Partridge: Infections due to Yeast-like Organisms.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 3 p.m., Professor J. Louw (Capetown): Indications for Caesarean Section.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor A. D. Gardner: Bacteriological Episodes.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr. D. F. O'Neill: Lecture-demonstration in psychiatry.

UNIVERSITY COLLEGE, LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, 5 p.m., public lecture by Professor J. R. Pappenheimer (Harvard): A Theory for Renal Haemodynamics.

Thursday, June 10

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, W., 8 p.m., Professor A. P. Cawadias: Psychological Factors in Graves's Disease.

EDINBURGH UNIVERSITY.—At Physiology Class Room, University New Buildings, 5 p.m., Dr. D. J. Guthrie: William Harvey: The New Outlook.

INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. Lawson Wilkins (Baltimore, U.S.A.): Endocrine and Non-endocrine Causes of Stunted Growth.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Pyogenic Cocci in Skin Disease.

●INSTITUTE OF NEUROLOGY—5.30 p.m., Mr. Harvey Jackson: Traumatic Intracranial Haemorrhage.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 12 noon, Professor J. Louw (Capetown): Surgical Emergencies in Pregnancy.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor H. S. Morton: Potentialities of the Electrogastrograph.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Lord Boyd-Orr, F.R.S.: Widening Field of Medicine.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., neurology demonstration by Dr. J. H. Paterson.

Friday, June 11

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. A. D. Porter: Pyococcal Infections.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. J. K. Monro: Some Observations on Urinary Stone. 4 p.m., Professor A. Bradford Hill, F.R.S.: The Clinical Trial.

ROYAL SANITARY INSTITUTE.—At Pump Room, Bath, 10.15 a.m., Dr. B. A. Astley-Weston: Personal Standards of Hygiene; Mr. A. Tyler: Chemical Agents and Poisonous Metals in Food.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Professor W. C. W. Nixon: Inertia in Labour.

Saturday, June 12

INSTITUTE OF ORTHOPAEDICS.—At Brockley Hill, Stanmore, 10 a.m., Dr. F. H. Stevenson: Teaching ward round.

NORTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At North Middlesex Hospital, Edmonton, N., 10.30 a.m., Mr. M. Bates: Thoracic Actinomycosis; Dr. J. V. Davies: Incidence of Tuberculosis in Schoolchildren and Their Contacts. 2 p.m., demonstration of clinical cases. 3 p.m., business meeting.

APPOINTMENTS

CHARING CROSS HOSPITAL.—Josephine Barnes, D.M., F.R.C.S., F.R.C.O.G., M.R.C.P., Consultant Part-time Assistant Obstetrician and Gynaecologist. P. B. S. Fowler, D.M., M.R.C.P., Consultant Part-time Assistant Physician.

EDGAR, WILLIAM, M.B., Ch.B., D.P.H., D.C.H., Deputy Medical Officer of Health and Deputy School Medical Officer, Borough of Luton.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Rosemary W. Lawrence, M.B., Ch.B., House-surgeon to Orthopaedic and Plastic Departments; Lilian F. Jones, M.B., Ch.B., M.R.C.P., House-physician; F. J. Hedden, M.B., B.Ch., F.R.C.S.Ed., Part-time Senior Registrar to Orthopaedic Department.

MCARTHUR, CATHERINE B., M.B., B.S., D.P.H., Medical Officer of Health, Oswestry Borough and Rural District Councils, and Assistant County Medical Officer, Salop County Council.

MACARTHUR, PATRICK, M.D., F.R.F.P.S., D.C.H., Consultant Paediatrician, Northern Regional Hospital Board (Scotland), Raigmore Hospital, Inverness.

NABARRO, J. D. N., M.D., M.R.C.P., Assistant General Physician, Middlesex Hospital, London, W.

SEAL, ROGER MARTIN EWART, M.B., B.Ch., M.R.C.P., Consultant Pathologist to Cardiff Hospital Management Committee (Sully Hospital).

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Heller.—On May 18, 1954, at Robroyston Hospital, Glasgow, to Betty, wife of Lieutenant M. D. A. Heller, R.A.M.C., a son.

Martin.—On May 27, 1954, at Sedan House, Stanley Place, Chester, to Dr. Rosemary (formerly Bolam), wife of Dr. Geoffrey Martin, a son.

DEATHS

Dewar.—On May 1, 1954, at Saxilby, Lincs, Thomas Dewar, M.B., C.M., aged 82.

Dudding.—On April 25, 1954, Thomas Scarbrough Dudding, O.B.E., M.R.C.S., L.R.C.P., D.P.H., Colonel, late R.A.M.C., retired, of Greestone Holme Lincoln, aged 75.

Elliott.—On April 28, 1954, at Oakburn, Toward Point, Dunoon, Argyll, William Marley Elliott, M.B., Ch.B., D.P.H., late of Glasgow.

Hendry.—On April 20, 1954, at Aberdeen Royal Infirmary, James Leith Hendry, M.C., L.R.C.P.&S.Ed., aged 66.

Lister.—On April 18, 1954, at his home, Seaford, Sussex, Septimus Rayner Lister, M.D., late of Terrington St. Clement, Norfolk.

Logg.—On April 20, 1954, at St. John's Hospital, Lewisham, London, S.E., Matthew H. Logg, M.D.

Lowe.—On April 28, 1954, Frederick Boulton Lowe, M.R.C.S., L.R.C.P., M.R.C.V.S., of 23, Pearl Court, Eastbourne, Sussex.

McCarter.—On April 19, 1954, at 2, Leigh Road, Havant, Hants, Frederick Buick McCarter, M.C., M.B., F.R.C.S.

McEwen.—On April 20, 1954, at the Oval, Doncaster, John Dugald McEwen, M.B., F.R.C.S.Ed.

Maclachlan.—On April 16, 1954, at Tigh-Na-Coille, Hunter's Quay, Argyll, Julia Crawford Maclachlan, M.B., Ch.B.

O'Donnell.—On April 27, 1954, at "Rostrevor," King's Avenue, Carshalton Beeches, Surrey, John David O'Donnell, M.B.E., F.R.C.S.Ed., late of Mysore Province, South India, aged 89.

Richmond.—On March 25, 1954, at his home, 5, Ruskin Terrace, Glasgow, Arthur Stanley Richmond, M.B., Ch.B., D.T.M.

Sturrock.—On April 27, 1954, at "Turlundie," Hillside Road, Radcliffe-on-Trent, Notts, George Sturrock, M.B., C.M., late of Woodborough Road, Nottingham, aged 87.

Thomas.—On April 24, 1954, Ellis Rae Thomas, M.D., of Kyrton House, Gillingham, Kent.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Vascular Effects of Pneumonectomy

Q.—*Please may I be informed of the effects of pneumonectomy on the vascular tree of the remaining lung in a young person, say aged 20 years? What type of occupation should such a person follow in the future, and is a cardiovascular cause of death a likely possibility?*

A.—This is a very pertinent question. No immediate ill effects of pneumonectomy are discernible on the vascular tree of the remaining lung of a young person, provided the lung is healthy. It has, for instance, been shown that the pulmonary artery pressure is unaltered; immediate compensation occurs.

Not enough time has yet elapsed for the very late results to be observed; the first successful pneumonectomies were done only 20 years ago. It is possible that no adverse changes occur if the remaining lung is not overdistended; if the mediastinum remains in the midline. Disability would be more likely to accompany progressive emphysema if this followed overdistension; this emphysema could be accompanied by secondary vascular degenerative changes leading to pulmonary hypertension and possibly secondary heart failure. This would be more likely if the remaining lung was not, initially, entirely healthy; if it had been damaged by non-tuberculous or tuberculous infection. The only direct evidence the writer has seen of the possibility of a late cardiovascular death was in the case of a man of 60 who was dying from right-sided heart failure and who had a lung agenesis. This was in some ways the equivalent of a pneumonectomy in infancy. The single lung was grossly overdistended and filling both sides of the chest.

A young adult, after pneumonectomy, should definitely avoid a strenuous occupation. Really hard physical work could be carried out for many years without obvious disability, but it would surely result in earlier onset of disability. The only wise thing is to select a sedentary occupation or one that does not involve regular physical work; in this way a long life free from disability is much more likely to be attained.

Masturbation in a Married Woman

Q.—*A happily married woman of 24, mother of two children, has recently been greatly distressed by an uncontrollable desire to masturbate. The habit began in early childhood and has recently returned, and a deeply satisfying orgasm always results, though this never follows normal coitus. I should be most grateful for your assistance in helping this patient.*

A.—This patient's condition is by no means ideal; but, in fact, it is not a very uncommon one, and, provided she understands the nature of her difficulty and conducts her marital life wisely, she need not fear any grave consequences. Most young children masturbate and many psychiatrists believe the activity to be part of normal development. Like this patient, many adult people fail, for varied and abstruse reasons, to reach a fully normal sexual development. When, therefore, orgasm cannot be attained in marital intercourse, it is not surprising that earlier outlets are sought. These situations are probably commoner in men than in women; they bring some difficulties in marital adjustment, just as do all other sexual inhibitions. Usually, perhaps, it is wisest not to tell the other partner, for the difficulty is not of his or her making. Since this woman is unable to get orgasm with her husband it is more normal for her to relieve the

sexual tension herself than to live in continual frustration. It is important, however, for the medical attendant to make sure that a common source of confusion is not being overlooked—that is, that the woman is not just suffering from vaginal anaesthesia and would be able to get clitoral orgasm by digital stimulation, were this not, for some reason, being withheld. If such should be the case, her husband must be instructed how to provide this so that she can achieve orgasm either before coitus or after, whichever suits the couple best.

Sterility of Mucous Membranes at Birth

Q.—*Are the mucous membranes of the nose and throat of a newborn baby sterile? If organisms are present, how did they establish themselves in a sterile amniotic cavity?*

A.—The nasopharyngeal mucous membrane of the newborn baby is sterile if delivery occurs soon after the membranes are ruptured—that is to say, before the liquor has had time to become infected. If, on the other hand, delivery is delayed a considerable time and the liquor does become infected, then inevitably the mucous membranes of the nose and throat of the baby are contaminated with the organisms infecting the liquor.

These organisms are a mixed flora and vary considerably. The commonest to be recovered from the baby's throat are coliforms (including *Proteus*), diphtheroids, staphylococci, and streptococci (both anaerobic and aerobic).

Scarring from Boils

Q.—*What can be done to improve the appearance of the back of a neck badly disfigured by pitting and scarring due to chronic furunculosis? The condition is now inactive, although the patient received a single course of superficial x rays for it about six months ago.*

A.—This is one of the most difficult conditions to treat. In the chronic stage, when it is often due to acne as well as to hair follicle infection—and as a rule evidence of infected hair follicles can be seen throughout the scarred surface—epilation by tweezer is a satisfactory method of keeping the infection down and allowing healing to become complete. Only after healing is complete should any surgical means be adopted, and even then it is only too often true that in many cases the scarring must be accepted. In particularly bad cases excision of the entire area and free grafting is the only alternative, but it should be a last resort, for the graft is certain to make a prominent white patch on the back of the neck.

Treatment of Leukoplakia of the Tongue

Q.—*I have a case of leukoplakia of the tongue which has been present for the past nine months. It started as quite a small area and is now almost the size of a halfpenny. It is quite superficial, and the Wassermann reaction and Kahn test are negative. I have given the patient large doses of vitamin A, and bland mouth-washes. In my student days the recommended treatment was excision. Will you please tell me the latest views on this condition and its treatment?*

A.—There has not been much change in our views on the treatment of leukoplakia of the tongue. Some surgeons have always been inclined to more radical measures than others. It is certain, however, that many cases of leukoplakia persist for years without showing any tendency to malignant change. In the present case, with a negative Wassermann reaction, the correct attitude is probably an expectant one.

All sources of irritation, such as irritant foods, dental sepsis, smoking, etc., should be eliminated, and a regular and careful watch kept for the appearance of papilliferous overgrowth, fissuring, or ulceration. At the first recognition of any of these a local excision should be done, preferably by diathermic cutting. It is best not to use any local application—for example, chromic or silver salts—but the normal mild antiseptic hygiene of the mouth and teeth should be continued. The presence of dissimilar metals in dentures and fillings which might set up an electrolytic couple should be looked for and corrected if necessary. Incidentally, lichen planus of the tongue, although rare, may closely resemble leukoplakia and must be excluded. It is usually of a lavender hue and there may be similar lesions on the skin.

Drowsiness in an Old Man

Q.—*What is the likely cause of drowsiness amounting to narcolepsy in an old man, with some prostate obstruction (but no elevation of the blood urea), auricular fibrillation, and early evidence of heart failure? He can fall asleep while eating a meal or standing up. There is no sugar or albumin in the urine. Can any treatment be recommended? Methylamphetamine hydrochloride and amphetamine have had little influence.*

A.—The presence of a normal blood urea and the absence of albumin in the urine do not, of course, exclude the possibility of renal failure being the cause of the drowsiness. However, the type of drowsiness is unlike that of renal failure in that it occurs when the patient is standing or eating a meal, as well as, presumably, at other times. This, as the questioner points out, is like true narcolepsy. It seems most likely that the drowsiness is due to a combination of cerebral arteriopathy and probably heart failure leading to a local ischaemia in the hypothalamic region, and thus to the symptoms of narcolepsy. In such a case methylamphetamine hydrochloride and amphetamine are unlikely to have much influence unless given in large doses, and treatment of the co-existing cardiac failure and anaemia, if any exists, is probably the most important factor in producing relief of the drowsiness. However, no great benefit from treatment can be expected in this case.

Plasma Potassium Estimation

Q.—*What is the simplest reliable method of estimating the plasma potassium?*

A.—Flame photometry is the simplest and most reliable method of estimating the plasma potassium, given a flame photometer and an experienced operator. In the absence of such facilities, the best method is cobaltinitrite precipitation, which is described in detail by King (*Micro-analysis in Medical Biochemistry*, Churchill, 1946). Samples of blood must be unhaemolysed, as the cells contain twenty times as much potassium as the plasma and contamination by cell content would lead to gross error; for the same reason, separation of plasma and cells should be done as soon as possible after withdrawing blood. It is also important to remember that the plasma potassium level may be misleading as an index of the state of potassium balance—for example, in diabetic coma the plasma potassium level may be high or normal until dehydration is corrected, although there is potassium depletion.

Correction.—In Table II in the paper on "Arsenamide Treatment of Filariasis due to *W. bancrofti* and *A. perstans*" by Drs. J. A. McFadzean and F. Hawking (April 24, p. 956) the weights of patients 19 and 23 ought to have been 51 kg. and not 31 kg. as printed.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London*. ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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